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HEPATIC COMA*

Clinical and Laboratory Observations on Forty Patients

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PROLONGED coma has been recognized as a frequent terminal event of both acute hepatic necrosis and chronic hepatic fibrosis. Frerichs,[1] in 1860, described the terminal mental changes in patients with acute yellow atrophy and with cirrhosis of the liver:

> Cases have occurred to me in which individuals who for a long period have suffered from cirrhosis of the liver, have suddenly presented a series of morbid symptoms which are foreign to that disease. They have become unconscious, and have been afterwards seized with noisy delirium, from which they passed to deep coma, and in this state have died. In most cases, slight jaundice made its appearance at the same time. . . .

Frerichs ascribed the mental symptoms to hepatic insufficiency with a decreased output of bile and termed the condition "acholia." Since that time little progress has been made in elucidating the pathological physiology of the condition, and confusion has arisen concerning the clinical features and laboratory findings. In this report attention is drawn to certain of the clinical manifestations, several etiologic factors are suggested, and the use of various therapeutic measures is evaluated.

Material

Forty patients were studied who died in coma and who both clinically and pathologically had severe primary liver disease. All were observed during life in the years 1945 and 1946. The coma, which occurred after a variable period of decreasing alertness and which lasted from twelve hours to six days, was the outstanding feature. No cases are included of metastatic liver disease, obstructive biliary-tract disease or massive gastrointestinal hemorrhage severe enough to cause death in shock. A number of otherwise acceptable cases were excluded because a pathological diagnosis was not made.

The cases so selected fall into two groups, equal in number: "uncomplicated" hepatic coma, in which no cause for death other than liver disease was found; and "complicated" hepatic coma, in which the patient had, in addition to severe liver disease, some major complication that may have played an important part in precipitating the coma (Table 1).

Pathological examination consisted of complete autopsy in 29, abdominal exploration and liver biopsy in 8, and punch biopsy of the liver in the remaining 3 cases. In the uncomplicated cases there were 15 of portal cirrhosis, 2 of healed acute yellow atrophy, and 1 each of subacute yellow atrophy, acute yellow atrophy and acute alcoholic hepatosis. In the group with complication there were 17 cases of portal cirrhosis, 2 of healed acute yellow atrophy, and 1 of advanced fatty metamorphosis of the liver.

Results

Uncomplicated Hepatic Coma

The 20 patients in this group, in whom no cause for death was found other than severe liver disease, were from thirty-five to seventy-two years of age with almost half in the sixth decade; 12 were men. Six of the patients denied the use of any alcohol, whereas 3 said that they had consumed no more than an occasional glass of beer or whisky. The remaining 11 admitted consuming at least 2 quarts of beer or a pint of whisky a day for years. Characteristically, they ate poorly when drinking. A summary of the pertinent findings in the history and

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physical examination is presented in Table 2. On admission 5 patients had been jaundiced for from one to eight weeks. Abdominal swelling for one week to eleven months was observed by 13 patients, of whom 4 had had an abdominal paracentesis before admission.

Patients with severe hepatic cirrhosis exhibit to a variable degree alteration in intellectual function and personality. Loss of affect and a defect senting increasing mental depression to the final stage of deep coma.

Although detailed neurologic examinations were not done, it was obvious that 17 of the patients presented some change in the state of consciousness on admission to the hospital, and in 7 cases mental or neurologic symptoms were the chief reason for admission. Six of these 7 patients admitted with lethargy, stupor or coma were dead

TABLE 1. *Identifying Data and Pathological Diagnoses in 40 Patients Dying in Liver Coma.*

CASE NO.	AGE	SEX	HISTORY OF CHRONIC ALCOHOLISM*	DURATION OF HOSPITALIZATION	DURATION OF COMA	PATHOLOGICAL DIAGNOSES	
						LIVER	ADDITIONAL
	yr.			days	days		
Uncomplicated coma:							
1	54	M	+	5	3	Laënnec's cirrhosis	Terminal bronchopneumonia
2	43	F	++++	9	3	Laënnec's cirrhosis	—
3	63	M	+	17	1	Healed acute yellow atrophy	Hypertensive heart disease
4	52	M	++++	17	6	Laënnec's cirrhosis	Terminal bronchopneumonia
5	66	M	0	11	5	Laënnec's cirrhosis	—
6	58	M	+	16	1	Subacute yellow atrophy	Chronic cholecystitis
7	59	F	0	17	6	Laënnec's cirrhosis	Duodenal ulcer; terminal bronchopneumonia.
8	48	M	++++	49	4	Laënnec's cirrhosis	Arteriosclerotic heart disease, decompensated
9	49	M	++++	60	1	Laënnec's cirrhosis	Rheumatic heart disease
10	70	F	0	15	2	Laënnec's cirrhosis	Terminal bronchopneumonia
11	57	F	0	5	1	Healed acute yellow atrophy	—
12	52	M	++++	150	1	Laënnec's cirrhosis	—
13	48	M	++++	75	4	Laënnec's cirrhosis	—
14	58	M	++++	100	5	Laënnec's cirrhosis	Healed bacterial endocarditis
15	52	M	++++	14	2	Laënnec's cirrhosis	Terminal bronchopneumonia
16	72	F	0	25	1	Laënnec's cirrhosis	Hypertensive and arteriosclerotic heart disease
17	63	M	+++	3	1	Laënnec's cirrhosis	—
18	35	F	++++	1	1	Acute alcoholic hepatosis	—
19	68	F	0	2	2	Acute yellow atrophy	—
20	46	F	++++	2	1	Laënnec's cirrhosis	—
Complicated coma:							
21	39	M	++++	1	1	Laënnec's cirrhosis	Pneumococcal pneumonia
22	50	M	++++	11	3	Laënnec's cirrhosis	Pneumococcal pneumonia
23	52	M	++++	2	2	Laënnec's cirrhosis	Pneumococcal pneumonia
24	50	M	0	1	2	Laënnec's cirrhosis	Pneumonia and meningitis due to Friedländer's bacillus
25	48	F	++	3	3	Laënnec's cirrhosis	Pneumococcal pneumonia
26	33	M	++++	1	1	Advanced fatty metamorphosis	Pneumococcal pneumonia
27	69	M	++++	3	3	Laënnec's cirrhosis	Pneumococcal pneumonia
28	50	F	++++	30	3	Laënnec's cirrhosis	Miliary tuberculosis
29	44	M	++++	7	5	Laënnec's cirrhosis	Miliary tuberculosis
30	52	M	++++	28	2	Laënnec's cirrhosis	Pulmonary tuberculosis
31	44	F	++++	12	12	Laënnec's cirrhosis	Miliary tuberculosis with meningitis
32	70	M	++++	3	3	Laënnec's cirrhosis	Rheumatic heart disease with bacterial endocarditis and meningitis
33	62	F	++++	11	3	Laënnec's cirrhosis	Acute bacterial endocarditis with meningitis
34	47	F	0	30	1	Laënnec's cirrhosis	Ruptured gastric varix
35	56	M	++	70	2	Healed acute yellow atrophy	Ruptured esophageal varix
36	60	M	++++	3	1	Laënnec's cirrhosis; primary hepatoma.	Cerebral metastases with hemorrhage
37	38	F	++++	106	6	Healed acute yellow atrophy	Peritonitis following insertion of peritoneal button
38	54	M	++++	120	2	Laënnec's cirrhosis	Peritonitis following insertion of peritoneal button
39	42	M	++++	45	4	Laënnec's cirrhosis	Peritonitis following insertion of peritoneal button
40	44	M	++++	12	2	Laënnec's cirrhosis	Peritonitis

*0 to ++++

in judgment are usually outstanding. Thus, the jaundiced, pot-bellied cirrhotic patients are usually the jovial clowns of the ward. Many of them leave the hospital time and again, insisting that they are perfectly well in spite of obvious edema, ascites and jaundice. At times, however, they are apathetic or negativistic. Hepatic coma takes its departure from this base line, variable as it is from patient to patient, and develops slowly through phases repre-

within five days; otherwise, there was no correlation between initial mental changes and duration of hospitalization, which ranged from one to a hundred and fifty days. Twelve of the patients in the entire group of 20 died within four days after admission, and only 5 were living after twenty days.

The changes in consciousness followed a rather constant sequence from lethargy to noisy confusion,

and finally to coma. Thus, lethargy and drowsiness marked the onset in 13 patients, who slept most of the time and were disinclined to eat or talk, but were easily aroused and were oriented as to person, place and time. An adequate intake of food could usually be maintained in this phase only by tube or parenteral feeding. The rate of progression of the mental changes was variable; in fact, several patients passed through one or more periods of drowsiness and confusion before coma ensued.

Confusion, characteristically noisy, superseded the period of lethargy after a few days to several weeks, although in 5 patients preceding lethargy was not observed. In 8 patients the confusion was minimal, at times being manifested by a harmless wandering, particularly at night. Frank hallucinations were distinctly rare. Hypnotics were given to most of the patients who exhibited this disturbed state, and in 10 patients were followed by a deep sleep, which merged imperceptibly into coma. Paraldehyde was the most frequently used sedative, being given to 7 patients. The dose, administered orally or intramuscularly, varied from 6 to 68 cc. given in from one to six doses. The largest individual dose was 14 cc., which was repeated in two hours. Of these 7 patients who received paraldehyde, 1 also received morphine sulfate and 1 a barbiturate. Because of severe abdominal pain, 1 patient received repeated doses of demerol, and 1, morphine sulfate. Another patient received repeated doses of paregoric because of persistent diarrhea.

Death occurred after twelve hours to six days of deep coma, although 14 patients died within the first two days. In our experience deep coma occurring spontaneously has invariably been fatal. The patients appeared as though they were merely sleeping, made no purposeful voluntary movements and responded less and less to painful stimuli. Thus, the comatose state was remarkable in the paucity of clinical signs other than the mental state, which almost alone distinguished it from the precoma period. The signs of liver disease remained essentially unchanged except for the appearance of clinical jaundice in 4 patients not previously jaundiced. Six patients were not jaundiced at death. The temperature, pulse and respiratory rate gradually rose during the coma, and in 5 patients the rise was associated with a terminal bronchopneumonia. Deep, regular respiration, particularly early in the coma, was one of the most characteristic observations. The blood pressure, usually normal or slightly low before the onset of coma, fell during coma and in 4 patients was below 90 systolic, 60 diastolic.

The pertinent laboratory data before and during coma are presented in Table 3. There was little change in the hemoglobin concentration (Sahli). The total white-cell count generally rose terminally so that it was below 5000 in only 2 cases, being between 10,000 and 20,000 in 6 and greater than 20,000 in 3. In spite of presumably adequate fluid intake, oliguria was the rule during coma and was reflected by a moderate rise in the blood nonprotein nitrogen concentration in the 15 patients in whom the determination was made. The plasma carbon dioxide combining power was usually moderately reduced, although in 2 patients somewhat high values were found. In half the patients the blood sugar (Folin–Wu method) was determined, and in no case was a dangerously low value found, the lowest being 68 mg. per 100 cc. The abnormally high values in 3 cases were found after recent intravenous dextrose or tube feeding.

TABLE 2. *Pertinent Findings on Admission in 40 Patients Dying in Liver Coma.*

FINDINGS	UNCOMPLICATED COMA*		COMPLICATED GROUP*	
	NO. OF CASES	PER-CENTAGE	NO. OF CASES	PER-CENTAGE
Anorexia	15	75	14	70
History of jaundice	5	25	9	45
Jaundice on physical examination	10	50	9	45
History of ascites	13	65	6	30
Ascites on physical examination	16	80	6	30
History of edema	10	50	5	25
Edema on physical examination	12	60	7	35
Abdominal pain	5	25	6	30
Palpable liver	9	45	13	65
Palpable spleen	3	15	2	10
Collateral abdominal veins	11	55	5	25
Spider angiomas	11	55	10	50
History of peripheral neuritis	5	25	4	20
History of hematemesis	3	15	2	10

*Each group comprised 20 patients.

As measurements of liver function, the serum bilirubin,[2] thymol turbidity,[3, 4] cephalin cholesterol flocculation[5*] and plasma prothrombin concentration[6*] were determined. Although these studies usually revealed evidence of severe liver disease, there were no consistent or striking changes between those made before and during coma (Table 3). The urine urobilinogen was extremely variable although in a few cases the nonurobilinogen Ehrlich-reacting substances[7] were increased in the urine to exceptionally high values.†

The blood alpha amino nitrogen concentration[8] was determined in 5 cases during coma, and values varied from 3.6 to 4.9 mg. per 100 cc. of serum, all within the normal range. Amino acid tolerance tests in 4 of these patients were previously reported and showed only slightly higher blood concentrations of alpha amino nitrogen four hours after the infusion than those of normal subjects.[9]

Blood tyrosol (free phenol) values were determined by the method of Bernhart and Schneider,[10] as modified by Roen,[11] and were found to be either normal or somewhat elevated but did not differ significantly from values obtained in the same pa-

*Determined at the Boston City Hospital Surgical Research Laboratory, Dr. Stephen J. Maddock, director.

†These urinary chromogens are poorly understood. The general term "urorosein" is used to designate them. Their chief constituent seems to be indol-acetic acid.

tients before coma or in other patients with cirrhosis not in coma. This is in contrast to a small group of patients with uremia in whom the values were consistently elevated, as reported by others.[12]

The spinal fluid was characteristically clear, under normal pressure and without cells. Small amounts of bilirubin (0.1 to 0.4 mg. per 100 cc.) appeared in the spinal fluid occasionally, with extreme jaundice (bilirubin concentration of from 13 to 20 mg. per 100 cc. of serum).

Admission orders for all conscious patients included a high-protein, high-calorie diet, which was supplemented with brewer's yeast (40 gm. per day), oral niacin (50 to 150 mg. per day) and subcutaneous thiamine (50 to 150 mg. per day). However, most of these patients ate poorly, and only 3 of the entire group of 20 were thought to be consuming an adequate diet at the onset of the coma.

Therapeutic measures during coma were directed toward the prevention of infection, especially bronchopneumonia, and the maintenance of the patient's nutrition.[13] In an effort to control infection, chemotherapeutic agents were used liberally, penicillin being administered to 14 of the patients in this group.

An adequate intake of nutrients during coma was provided either by stomach tube or parenterally, or both. Although the possibility of inducing bleeding from esophageal varices by a stomach tube (Levin type) exists, we have never seen this complication. Tube-feeding formulas made use of either an eggnog* or a mixture of milk and a liver protein preparation.† They were well tolerated.

Parenteral dextrose in amounts from 1 to 3 liters daily and in concentrations of from 5 per cent to 20 per cent was administered to 14 of the 20 patients. Vitamins C, K and the B complex (thiamine, riboflavin, nicotinamide, pyridoxine and pantothenic acid), prepared for parenteral use, were usually added to the dextrose solution. The daily intake of these vitamins was usually very high, 1 or 2 ampoules‡ being used daily. In addition, each patient received from 50 to 150 mg. of thiamine, subcutaneously, daily. Six of the patients were given 10 or 20 cc. of unrefined liver extract daily in the intravenous infusion mixture. Two liver-extract preparations were used, one a standard preparation§ and the other¶ prepared specifically for intravenous use.[15] Both preparations were well tolerated, neither flushing nor pyrogenic reactions being observed with the method of administration used. In a few patients very large amounts (50 to 100 cc.) of the latter preparation were administered. No

TABLE 3. *Laboratory Data in Patients Dying in Uncomplicated Liver Coma.*

Case No.	Hemoglobin		White-Cell Count		Blood Nonprotein Nitrogen		Blood Carbon Dioxide Combining Power		Blood Sugar	
	On admission*	During coma*	On admission*	During coma*	On admission*	During coma*	On admission*	During coma*	On admission*	During coma*
	%	%	x10³	x10³	mg./100 cc.	mg./100 cc.	vol. %	vol. %	mg./100 cc.	mg./100 cc.
1	104	—	17	22	25	44	—	31	—	—
2	58	54	9	8	25	35	—	46	110	235§
3	98	—	8	11	31	65	—	31	110	—
4	58	60	6	19	29	70	42	45	99	110
5	53	58	5	9	30	31	32	32	123	123
6	91	95	8	9	31	82	—	—	—	100
7	75	—	5	22	33	45	45	36	—	144
8	78	—	8	18	36	70	—	25	114	—
9	75	68	4	4	25	74	44	34	100	—
10	48	75	5	14	37	39	41	—	—	—
11	77	70	8	—	27	57	—	—	—	—
12	78	—	6	—	28	—	—	—	—	—
13	80	120	5	32	25	52	—	40	—	95
14	80	—	9	—	34	40	—	—	—	—
15	72	73	12	15	25	63	—	27	—	82
16	95	88	3	4	26	47	—	40	—	—
17	—	63	—	8	—	34	—	68	—	190§
18	—	84	—	16	—	80	—	44	—	—
19	—	95	—	9	—	98	—	55	—	68
20	—	55	—	6	—	28	—	61	—	300§

*The intervals between the data on admission and those obtained during coma are shown in Table 1.
†Icteric index of 35.
‡Icteric index of 75.
§Shortly after intravenous administration of dextrose.
¶Icteric index of 85.
‖Icteric index of 90.

*One quart contains 700 cc. of whole milk, 3 eggs, 40 gm. of sugar and 150 gm. of skimmed-milk powder.

†"Ledinac," [14] furnished by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

‡"Solu-B" (furnished by the Upjohn Company, Kalamazoo, Michigan), containing 10 mg. of thiamine, 10 mg. of riboflavin, 5 mg. of pyridoxine, 50 mg. of calcium pantothenate and 250 mg. of nicotinamide. "Betasymplex" (Winthrop), containing 10 mg. of thiamine, 5 mg. of riboflavin, 5 mg. of pyridoxine, 5 mg. of calcium pantothenate, and 50 mg. of nicotinamide.

§Solution Liver Extract crude, Lilly; 2 injectable U.S.P. units per cubic centimeter provided by Eli Lilly and Co., Indianapolis, Indiana.

¶"Intraheptol," provided by Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York.

change in clinical condition that could be attributed to this form of therapy was observed.

From 45 to 100 gm. of one of two protein hydrolysate solutions* were added to the intravenous infusions of 8 of the 20 patients. No pyrogenic reactions or apparently harmful effects were observed from the administration of these preparations in the presence of severe liver disease. In fact, as mentioned above, amino acid "load tests" have given no evidence of a significantly reduced tolerance in patients with severe liver disease as compared with that in normal persons.[9]

Central-nervous-system stimulants and analeptics were given to many of the patients. Caffeine, benzedrine (amphetamine) sulfate and picrotoxin in moderate amounts subcutaneously or intravenously did not induce a response. In view of the reported effectiveness of sodium succinate in barbiturate narcosis[16, 17] 30 gm. of this substance† was administered intravenously over a period of one hour to each of 2 patients. Marked flushing and tachypnea occurred, but no therapeutic effect was observed. Rapidly infused concentrated dextrose solution (usually 100 cc. of a 50 per cent solution) failed to alter the state of coma in all but 1 patient. In this patient the coma became temporarily lighter but was then refractory to the further administration of dextrose.

*"Amigen," furnished by the Mead Johnson Company, Evansville, Indiana; "parenamine," furnished by Frederick Stearns and Company, Detroit, Michigan.

†"Soduxin," furnished by Brewer and Company, Incorporated, Worcester, Massachusetts.

Complicated Coma

Although the 20 patients in this group all died in coma and at autopsy had severe liver disease, they are considered as a separate group because each was complicated by another major pathologic state (Table 1): Seventeen patients had severe infection. Seven patients had pneumonia, 4 tuberculosis (in 3 of whom the disease was miliary), 4 peritonitis (in 3 secondary to the insertion of a peritoneal button[18]), and 2 bacterial endocarditis. Two patients lapsed into coma after bleeding from esophageal varices although there was no clinical evidence of shock. One patient had a hepatoma superimposed on Laënnec's cirrhosis. The mental symptoms in this case may have been due to cerebral metastases. The historical data and physical findings concerning this group of patients are presented in Table 2. The lesser incidence of ascites, edema and collateral abdominal veins in the complicated group is evident.

The development of coma in these patients was an accelerated version of that seen in the uncomplicated group. In 8 patients the liver disease was far advanced and clinically indistinguishable from that encountered in the uncomplicated group. In the remaining 12 there was severe liver disease, but the complicating infection or hemorrhage was obviously the chief difficulty. It appeared as though the complicating factor had precipitated the terminal coma before it would have occurred in the natural course of the liver disease alone.

TABLE 3 (*Continued*).

Case No.	Serum Bilirubin				Blood Prothrombin Content		Serum Thymol Turbidity (Barium Sulfate Suspension)		Serum Cephalin Flocculation	
	Prompt Direct on Admission*	Total on Admission*	Prompt Direct during Coma*	Total during Coma*	on Admission*	during Coma*	on Admission*	during Coma*	on Admission*	during Coma*
	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	%	%	cc.	cc.		
1	—	†	—	‡	40	—	—	—	0	—
2	0.4	1.4	0.3	1.1	80	—	3.5	4.5	—	—
3	0.2	1.9	0.3	1.7	58	72	2.9	3.1	++++	++++
4	2.0	4.0	6.2	9.4	78	38	0.4	0.4	0	+
5	—	¶	—	‖	70	—	—	—	+++	—
6	—	—	2.3	8.5	37	10	—	0.9	+	++++
7	—	—	1.3	3.9	75	45	—	4.5	++++	—
8	0.5	0.8	0.4	0.6	90	—	—	2.0	++	—
9	1.5	4.3	1.0	2.5	48	42	3.2	2.5	++++	+++
10	0.4	1.2	0.7	2.3	75	75	1.5	1.5	++++	+++
11	0.4	1.0	0.8	1.9	87	—	2.5	2.4	++++	—
12	0.2	0.5	0.8	1.8	43	8	1.8	3.5	0	++
13	1.5	3.4	0.6	3.8	49	48	1.7	3.0	+++	+++
14	0.3	1.4	0.3	1.6	85	90	2.2	2.4	++++	++++
15	1.9	3.8	1.3	2.7	43	95	4.9	2.8	++++	+++
16	0.3	1.1	0.9	2.4	75	60	4.3	4.3	++	++++
17	—	—	5.7	17.3	—	40	—	2.5	—	+++
18	—	—	18.5	25.2	—	25	—	1.6	—	0
19	—	—	4.7	7.4	—	10	—	2.6	—	—
20	—	—	8.2	17.5	—	65	—	4.4	—	++++

The laboratory data were essentially the same as those in the uncomplicated group except for the presence of bacteremia in 6 cases. The white-cell count was not a reliable index of infection, being above 12,000 in only 6 patients and below 5000 in 5. Moreover, the white-cell count was frequently high in the uncomplicated cases.

Hypnotics and analgesics were administered to 8 patients in this group, and in some cases undoubtedly contributed to the development of coma. Paraldehyde was used in 7 patients in amounts of 6 to 96 cc. over a period of a few hours to several days. Demerol was combined with paraldehyde in 1 case, as was morphine sulfate in another. One patient became comatose after 225 mg. of demerol given in three doses over a period of twelve hours.

In addition to the therapeutic measures used for the patients with "uncomplicated" coma, vigorous treatment of the complicating factor was undertaken. Appropriate chemotherapeutic agents were administered. Sulfonamides (usually sulfadiazine) were not withheld because of liver disease if their use was indicated but were administered cautiously as recommended by Peterson, Deutsch and Finland.[19] Blood transfusions were used after acute blood loss from bleeding varices. That these therapeutic measures are occasionally effective is suggested by the fact that in the two years covered by this study, 4 patients with cirrhosis, not included in this study, recovered from coma. The coma in 2 was accompanied by severe infection and in 2 was associated with sedation.

Discussion

Since Frerichs's description, presented above, many attempts have been made to define both clinically and etiologically the coma in patients with liver disease. Leyden,[20] in 1866, noted a clinical resemblance of liver coma to kidney failure and suggested the term "cholemia," ascribing the coma to a retention of bile acids in the blood. This terminology has persisted, although the underlying concept has been generally discredited. Indeed, complete biliary obstruction is compatible with long periods of comparatively good health, and, in contrast, liver disease may terminate in coma with only minimal bile retention (Tables 2 and 3). Spence and Ogilvie,[21] in 1927, reported terminal "cholemia" in 21 cases of acute yellow atrophy of the liver, but were unable to elucidate the etiology on the basis of their clinical findings.

No specific clinical finding other than coma served to distinguish the comatose state in our patients. The patients appeared to be sleeping but could not be aroused. The presence of liver disease was usually obvious from the history and physical examination, although jaundice was not always present. Respirations were usually regular although commonly increased in depth and rate. Neurologic findings were likewise nonspecific.

The results of the usual laboratory tests were neither characteristic nor of help in elucidating the pathogenesis of the condition. Greene[22] similarly noted the lack of significant blood chemical changes. The terminal rise in blood nonprotein nitrogen observed could be correlated with oliguria, which was usually present in spite of an adequate fluid intake.[23–26] Our results do not indicate which fraction of the blood nonprotein nitrogen rises, except that it is not alpha amino nitrogen. Maddock[27] found a high undetermined fraction of blood nitrogen in hepatectomized monkeys. Croftan[28] suggested, in 1906, and others have subsequently concurred, that after liver damage the blood is flooded with "toxic" products of incomplete protein breakdown. The occurrence of mental symptoms and coma in Eck-fistula dogs fed high meat rations supports the toxin theory,[29] although others believe the cause in this instance to be an incidental infectious encephalitis.[30] The possibility that a toxic compound from altered protein breakdown, especially from the aromatic amino acids, might be found in the blood phenol fraction led us to measure the free phenol concentration. As with other blood constituents, any abnormality found (a rise in this case) was no greater in liver coma than in patients with severe liver disease not in coma. Thus, in spite of a long-continued search for a metabolic toxin in liver coma none has been demonstrated. In fact, Greene[22] has suggested that it is unnecessary to postulate a "toxin" to explain coma in disease of an organ with as profound biochemical importance as the liver.

Our patients failed to show significant hypoglycemia; however, most of them were given carbohydrate by mouth or glucose parenterally, both before and during coma. In only 1 case did the coma become significantly lighter in response to rapidly infused concentrated dextrose, and then the response was only transitory. Thus, the coma in these patients is not analogous to the hypoglycemic coma that develops in hepatectomized dogs and responds dramatically to the parenteral administration of glucose.[29, 31]

Recently, Snell and Butt[32] observed increased amounts of lactic and pyruvic acids in the blood of patients with liver coma and noted a clinical response to administration of parenteral glucose, niacin and thiamine. They postulated that coma in hepatic disease is due to an abnormality of carbohydrate metabolism related to deficiencies of these vitamins. Patek[33] has confirmed the beneficial effect of the administration of glucose and vitamins. Simple vitamin deficiencies did not appear to be responsible for the coma in our patients since large supplements were given to all, both before and during coma. However, the observation of Williams and Bissell[34] that in patients with liver disease the formation of cocarboxylase from thiamine is impaired indicates a metabolic abnormality in these pa-

tients that may explain the high blood pyruvate found by Snell and Butt.[32] It seems likely that this and other biochemical abnormalities exist in patients with liver disease and may play an important role in the genesis of coma.

Although the metabolic defects responsible for coma in liver disease have not been explored, the etiologic importance of infection, hemorrhage and sedatives is clear; the first two, at least, may be amenable to specific treatment.

Infection was the single most common known factor in the precipitation of coma in our series, being considered of major importance in 17 patients. The coma so produced was indistinguishable from that developing spontaneously. The exact nature of the influence of infection upon the metabolic processes of the liver is not known. Fever itself may cause hepatic necrosis, which is evidenced clinically by jaundice and bromsulfalein retention.[35, 36] Furthermore, jaundice occurs in a small percentage of patients with pneumococcal pneumonia, especially in pneumonia complicated by septicemia, and is thought to be due, at least in part, to liver damage.[37] Beeson et al.[38] have demonstrated that the hepatic-vein blood in cases of endocarditis contains strikingly fewer bacteria than either peripheral venous or arterial blood, suggesting that the liver is a major site of removal of circulating bacteria. The possibility of concentration of bacterial toxins in the liver thus exists. The pneumococcus, tubercle bacillus, and gram-negative organisms from the gastrointestinal tract were the bacterial agents responsible for the infections encountered in our patients; however, little is known of the effect upon the liver of the toxins elaborated by these organisms.

In patients with "medical shock" due to severe infections, indications of damage to the liver have been observed both clinically and pathologically.[39] The profound circulatory changes that occur with infections and fever[40] may diminish the oxygen supply to the liver and may thus be comparable to the situation following hemorrhage, as pointed out below.

Acute hemorrhage from ruptured esophageal varices precipitated coma in 2 of our patients. Recent studies on the effect of acute blood loss have shown a greater reduction in portal blood flow than is suggested by changes in the systemic blood pressures, and further that the oxygen content of the portal blood is also markedly decreased.[41–44] Since the liver receives from 75 to 80 per cent of its oxygen from the portal system, marked hepatic anoxia might be expected from severe hemorrhage, and, according to the observations of LePage,[45] depletion of adenosine di-phosphate and triphosphate would occur.

In addition to infection and hemorrhage, the injudicious use of sedatives was a factor in the production of coma in our patients. In some cases it was clearly the major factor, whereas in others it appeared only to be contributory, being given during the phase of excitement and serving to hasten the appearance of coma. Most forms of sedatives seem to be poorly tolerated by patients with liver disease. This is especially true of morphine and other alkaloids.[46] Fagin and Thompson[47] observed that of 15 patients dying in liver coma, the coma in 6 followed the administration of morphine by a few hours. In fact, as little as 10 mg. of morphine sulfate may induce coma lasting up to three days or until death supervenes. There is little or no evidence that small doses of morphine actually damage the liver, but it is probable that with liver disease the body is less able to get rid of the drug, since a portion of administered morphine is conjugated in the liver with glucuronic acid.[48–50] After experimental liver damage the excretion of free morphine is increased and that of the glucuronide decreased.[51, 52]

Many of the barbiturates are likewise poorly tolerated in patients with liver disease.[53] Like morphine, most are in part, if not largely, destroyed, conjugated or excreted by the liver (especially amytal, pentobarbital, seconal and evipal).[54–56] Barbital and phenobarbital are to a greater extent eliminated by the kidney but, although probably safer than the others, are not without danger. Paraldehyde has been a favorite hypnotic for use in alcoholism and, because of the frequent concurrence of the two conditions, has often been used in patients with liver disease. In our experience, however, it may be highly dangerous. Levine[57] has shown in animals that the drug is metabolized largely by the liver and that it persists in the blood of both men and animals for long periods when liver damage is present. The problem of providing adequate sedation or analgesia in patients with severe liver disease is, indeed, a difficult one, and at present there does not appear to be a satisfactory solution. Although the danger of sedatives in liver disease must not be overlooked, it should be pointed out that patients to whom sedatives have not been administered also develop coma.

Summary

The clinical and laboratory studies on 40 patients with severe primary liver disease who died in coma are presented. Liver coma is a distinct clinical syndrome characterized by a progression from lethargy to noisy confusion, to coma and usually to death. The syndrome occurs in patients with severe liver disease, either spontaneously or as the result of infection, hemorrhage or sedation. In half the patients, the coma was precipitated by infection (17 patients), acute hemorrhage (2 patients) or cerebral metastases (1 patient). Central-nervous-system depressants have a prolonged action in patients with liver disease and in this way are believed to play an important role in the genesis

of liver coma. Aside from evidence of severe liver disease, the physical examination and laboratory findings during coma are not distinctive nor are they significantly different from precoma findings. Treatment, which is generally unsatisfactory, is directed at maintenance of nutrition, control of infection or hemorrhage and avoidance of sedatives. Analeptics, including glucose, sodium succinate, caffeine, and benzedrine, are without effect upon the comatose state.

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THE USE OF BRILLIANT GREEN IN THE TREATMENT OF CHRONIC ULCERS OF THE SKIN

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THE multiplicity of treatments reported in the literature on the subject of chronic ulcers of the skin is evidence that no one treatment has adequately met the required standards of being bactericidal, nontoxic, stimulating to the growth of epithelium and granulation tissue, giving prompt, effective and uniform results and being cheap and easy to use. During a tour of duty with the Army in the Pacific Theater of Operations, I had occasion to see a number of cases of chronic skin ulcerations, of varied etiologies. Each of these cases was treated with the rosaniline dye, brilliant green, and the results obtained indicate that this drug is the one that most nearly meets the stated requirements.

Chemically, brilliant green, like gentian violet, crystal violet and methyl violet, is a derivative of triphenylmethane. These rosaniline dyes are inhibitory to the gram-positive micro-organisms, particularly staphylococci, *Corynebacterium diphtheriae* and *Pseudomonas aeruginosa*. Brilliant green, though employed sporadically for many years because of its sterilizing properties, is not an official drug as yet. It has received trials in the treatment of erysipelas and leprosy, and, in recent years, Aldrich[1] has combined it with gentian violet and acriviolet in his triple-dye treatment of burns. The dye has been used most frequently in bacteriologic staining and can be obtained in the form of a green powder, which is readily soluble in water and alcohol.† Narat,[2, 3] who has written extensively about brilliant green, claims that the aqueous solution is not stable, but in my experience this is not true, inasmuch as stock aqueous solutions continued to give excellent clinical results months after their preparation.

Brilliant green was used in over 20 cases of chronic ulceration of the skin. It is realized that this series is too small to justify extensive conclusions, but the results were so uniform and so excellent in all cases that it was decided to present them in the form of a preliminary report in the hope of stimulating further investigations regarding its use. In all cases, the dye was used as a 2 per cent solution in distilled water. After thorough cleansing of the ulcer with hydrogen peroxide and alcohol, the dye was painted on daily until healing was progressing well — generally about seven to ten days. It was then applied every other day until healing was complete. The ulcer was covered with a dry sterile dressing after each treatment. The patient was advised to rest as much as possible and to sleep with the affected extremity elevated. Otherwise, no instructions or treatments were given.

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†Manufactured by National Aniline Division, Allied Chemical and Dye Corporation, New York City.

CASE REPORTS

CASE 1. M. J. R., a 25-year-old Filipino merchant seaman, was first seen in November, 1947, complaining of a large, rapidly progressing ulcer on the dorsum of the right foot (Fig. 1). About 1 month prior to his first visit his foot had

FIGURE 1. *A Chronic Ulcer of One Month's Duration before Treatment.*

been bruised by a steel cable, and the resulting small wound became infected and quickly broke down. Upon examination the ulcer measured 3.8 by 3.3 cm.; the base was deep and was covered with dirty, evil-smelling, necrotic tissue. No evidence of healing was seen. Pain was moderate. The patient was

FIGURE 2. *Ulcer after Five Applications of Brilliant Green.*

placed on hot soaks, bed rest and elevation of the leg for a 2-day period, with no change in the appearance of the lesion except that the size of the wound had increased slightly. Brilliant green was applied. After one treatment with the dye, the necrotic exudate had lessened considerably, the odor had practically disappeared, and evidences of healing were already present. The pain and discomfort in the wound were completely gone. After only five applications of the dye, the necrotic exudate had disappeared, the base of the wound was level with the surrounding skin and was composed of clean,

healthy granulation tissue, and epithelium was growing rapidly at the edges. The wound now measured 3.3 by 2.6 cm., having closed 5 to 7 mm. in less than 1 week (Fig. 2). Healing progressed rapidly and steadily so that on the 26th day of treatment, after eighteen applications of brilliant green, healing was complete and the skin surface intact (Fig. 3). Follow-up examination 1 month later showed no evidence of recurrence.

FIGURE 3. *Ulcer Completely Healed on the Twenty-Sixth Day of Therapy, after Eighteen Applications of the Dye.*

CASE 2. L. R., a 10-year-old Filipina, first appeared early in December, 1947, with a large, deeply excavated tropical ulcer over the medial malleolus of the left leg (Fig. 4). It had started 3 months before as a slight scratch, which had become infected and had grown progressively larger and deeper. She had received intensive treatment with hydrogen peroxide soaks, sulfanilamide crystals and locally applied neoarsphenamine before coming to the clinic, without retarding the progress of the lesion. Upon examination, the

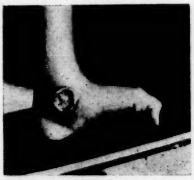

FIGURE 4. *A Tropical Ulcer of Three Months' Duration before Treatment.*

wound measured 3.4 by 3.0 cm., and the edges were markedly indurated. The base was 4 mm. below the skin surface and was covered with the same type of slimy, malodorous, necrotic discharge as that in Case 1. Pain was marked, especially at night. After one application of the dye, the pain was gone, the swelling and induration about the ulcer had lessened, the base of the wound was starting to fill in, and the exudate, though still profuse, was no longer foul smelling. After eleven applications of brilliant green, the surface of the ulcer was completely level with healthy granulations, and epithelization was progressing rapidly. The ulcer now measured 1.5 by 1.8 cm., a closure of more than 70 per cent of the surface area. There was no exudate (Fig. 5). Healing continued to be rapid, and after 29 days of treatment, which comprised 17 applications of the dye, the patient was discharged with the ulcer healed (Fig. 6). Six weeks later, she returned for a follow-up visit. The ankle looked perfectly normal, and there was no evidence of regression (Fig. 7).

CASE 3. C. D., a 53-year-old man employed as a merchant seaman, appeared in the clinic in August, 1947, for the first time, complaining of an infected ulcer over the anterior surface of the left tibia of 1 week's duration. The patient gave a history of mild diabetes mellitus, which was kept under control by dietary measures. His cardiovascular history was completely negative. He had struck his shin 1 week before, received an abrasion that refused to heal, rapidly became infected and then ulcerated. Physical examination revealed the heart to be normal, and there was no glycosuria on repeated examinations. On his left leg he had a circular wound, 2.5 cm. in diameter, covered with a scab. Removal of the scab exposed a shallow, dirty, infected ulcer showing no signs of healing. Both legs were covered with numerous scars, the results of previous leg ulcers similar to the present complaint. None of these had healed in less than 3 months' time. The patient was treated with hot soaks, thorough daily cleansing, zinc oxide ointment and sterile dressings for 1 week. At the end of this period, the infection had subsided somewhat, but

FIGURE 5. *Progress of Healing after Eleven Applications of Brilliant Green.*

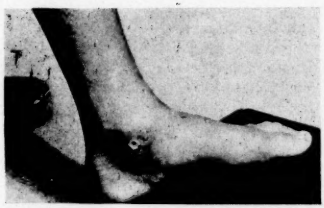

FIGURE 6. *Healing of the Ulcer on the Twenty-Ninth Day of Therapy, after Seventeen Treatments with the Dye.*

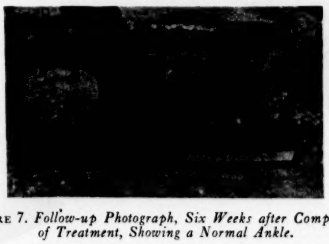

FIGURE 7. *Follow-up Photograph, Six Weeks after Completion of Treatment, Showing a Normal Ankle.*

the size of the wound was unchanged and no healing tendency was noted. Brilliant green applications were then started, and other treatments suspended. Improvement was noted almost immediately and the ulcer was completely healed 16 days later, after fourteen applications of the dye.

CASE 4. S. L., a 32-year-old Filipino man employed as a clerk, was first seen in September, 1947. Almost 4 months before, he had developed a carbuncle on the left side of his abdomen. He received no medical attention, and the carbuncle gradually emptied of itself. One month after onset, it had become an indolent, nonhealing ulcer. On first examination, the ulcer measured 2.3 by 2.4 cm. and was moderately infected. It was shallow, but the base showed no clean granulations. Brilliant green applications were started at once, and 1 day later, evidences of healing could be noted. In 11 days, after only seven dye applications, the ulcer was completely healed, and the patient discharged. Follow-up examination 2 months later showed no recurrence.

DISCUSSION

Brilliant green, a rosaniline dye of the triphenylmethane series, seems to offer many advantages in the treatment of chronic, indolent ulcers of the skin. It is bactericidal for many of the common pathogenic bacteria, has a high stimulating effect on the growth of epithelium and granulation tissues and counteracts the malodorous discharge common to this type of case. It is completely nontoxic, does not irritate tissues and has the added advantage of being low in cost. It can be as easily used in the doctor's office or the patient's home as in the hospital clinic. The staining of normal skin that occurs incident to its use can be removed readily by washing with alcohol.

SUMMARY

Experiences in a limited series of cases of chronic skin ulcers with a 2 per cent aqueous solution of the rosaniline dye, brilliant green, are presented.

The advantages of brilliant green — its bactericidal action, its stimulative effect on epithelium and granulation tissue, its nontoxicity, cheap cost and ease of application — are cited.

It is believed that the use of brilliant green merits further trials in the treatment of all types of chronic ulcers of the skin.

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THE RELATION BETWEEN THE INDUSTRIAL PHYSICIAN AND THE FAMILY DOCTOR*

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DURING the decade from 1911 to 1920 all but a handful of states enacted workmen's compensation acts and thereby brought into being that peculiarly hybrid creature, the industrial physician. Back in those early days the propriety of entering such a low-born specialty was questionable, and there can be no doubt that a number of poorly qualified doctors entered this field. There were in addition, however, men of unquestioned ability and integrity, and as pioneers in a new and uncharted field they endured the scorn and insults of other doctors, and at the same time they evolved the fundamental knowledge and procedures that now form the basis of industrial medicine, a specialty today in its own right. In general the relations between the industrial physician and the general practitioner are now harmonious, but there is still room for improvement, and there are probably justifiable complaints on both sides.

I should like to pause here for a moment to define roughly my own ideas of what constitutes an industrial physician and his job. An industrial physician should in the first place be a well trained, capable and honest doctor. As Professor Philip Drinker has often expressed it, a doctor is not good enough to care for the employees of a plant unless he is also good enough to care for the boss and the boss's family. The industrial physician must in addition have an interest in the employees in health as well as in sickness. Far too common is the self-styled industrial doctor who is nothing but a "patcher-upper"; this man usually knows nothing about the workings of the plant, the materials employed, the procedures carried out or the nature of the actual jobs performed by the workers. How can a doctor carry out a routine pre-employment physical examination if he doesn't know intimately the demands and requirements of the job in question? In the year or so following the war I had the opportunity of talking with a large number of young doctors just out of the service who were looking for industrial jobs. Actually all but a tiny minority were looking only for a sort of insurance job, bits of traumatic surgery with fees guaranteed. They had not the slightest interest in supervising the well-being of the healthy worker and in trying to keep him that way.

Last year at the Atlantic City meeting of the American Medical Association Dr. Poole,‡ of the Lockheed Aircraft Corporation, gave a paper on this

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‡Poole, E. E. General practitioner as adjunct to industrial surgeon. *Occup. Med.* **4**:293-304, 1947.

same general subject. Without any question he stole much of my thunder, but running in second position I have the opportunity of re-emphasizing many of his points. In one particular I shall undertake to split a hair. Dr. Poole chose as his title, "The General Practitioner as an Adjunct to the Industrial Surgeon." I should prefer to put the shoe on the other foot and state that the industrial physician — or surgeon — is more properly an adjunct to the general practitioner. Regardless of who gets top billing, the aim of both is exactly the same, and they must be regarded as collaborators. Let us briefly consider this point. The family doctor, or any physician in private practice for that matter, ordinarily sees his patients only when they are sick or ailing. When he does see them his natural desire, unless he is a charlatan, is to restore them to health as quickly as possible. In other words, he wants to get the patient back to a normal productive life as soon as it is safe and proper. This is naturally of particular importance if the patient is the wage-earner for a family. The industrial physician has exactly the same idea; he is perhaps more concerned with keeping the well person healthy and in protecting the handicapped person from further damage. His purpose, his *raison d'être*, therefore, is to keep the human element in industry efficient and productive. Naturally this is advantageous to the industry and its management, but it is even more of a boon to the individual.

Only 10 per cent of the total time lost in industry because of sickness is the result of occupational disease or industrial injury. The industrial physician who interests himself solely in the care of injuries is no more than nibbling at the corner of the problem. He is obligated to consider all phases of the employees' make-up just as much as the family doctor must give thought to the occupational aspects of his patients' histories. Your work and mine, therefore, overlap, and where they do not overlap, they supplement one another. Let us consider a few specific situations in which general medicine and industrial medicine do overlap and in which apparent differences of opinion arise.

First of all there is the problem of the preplacement physical examination. This is one of the first contacts that a new worker makes with his future employer. The examining physician assumes that the man is healthy — at least he walked in under his own steam ready to go to work. Unlike the hospital physical examination, abnormal findings here come usually as a surprise. The preplacement examination is brief but more searching than one might think. The findings are considered not as pathologic entities but as they relate to the specific job the man is to do; the requirements for a draftsman and an outdoor laborer obviously are not the same. Occasionally it will become apparent that a man's physical condition and his job do not go together, and the doctor has to say, "No, it would be a serious mistake to permit this man to do this type of work — he might be able to do some other job, but he can't do this one." In many cases the man himself is unaware of the significance of his disability, and he feels hurt, not to say insulted.

Nobody wins if a man is permitted to go to work on a job for which he is unsuited; it is the responsibility of the examining physician to keep the square pegs out of the round holes. Frequently, a disappointed worker goes straight to his family doctor, and that is just where he should go; more often than not it has been suggested by the examining doctor that he make the visit. You would be astonished at the number of perfectly reputable physicians who disregard entirely the warnings of the plant physician and argue heatedly that the man *is* able to go to work, even though they have little or no idea of the precise nature of the work and its demands.

Physicians doing a good deal of examining for large industries become fairly proficient in discovering the elusive hernia. One would think that most doctors would be somewhat guarded in flatly contradicting the statement of an experienced examiner that a definite hernia has been found, and yet that is done repeatedly. It might be mentioned that the outpatient departments of the large hospitals, where the examinations are performed by relatively inexperienced house officers, are particularly frequent offenders in this regard. I am frank to admit that at no time in my hospital experience have I ever learned how to find hernia except one visible at ten paces.

The pre-employment — or preplacement — examination is an ideal opportunity to discover pathology in its earliest stages. I can think of no more common-sense form of preventive medicine, and I have enough faith in the profession to believe that every doctor would prefer to have one of his own patients come to him with a condition easily correctible rather than something neglected and beyond repair. Sometimes one wonders even about that; we recently sent a man back to his family doctor after a chest x-ray film had revealed a suspicious apical shadow. This doctor was utterly scornful and said that the patient could not have tuberculosis, since he had neither cough nor loss of weight.

Local practitioners are frequently critical in claiming that industrial clinics offer *treatment* for non-industrial conditions. In my own clinic approximately 20 per cent of our total visits are listed as being for nonindustrial complaints, and this seems to bear out the criticism. However, most of these visits are for heartburn, runny noses, headaches, hangovers, nosebleeds, diarrhea and similar trivialities. These are not problems that send a person to his family doctor — they are the conditions that send the child to and are treated by its mother (not the hangovers, perhaps). If we should deny attention to these people they would not go to their doctors — they would go if anywhere to the corner drugstore. I contend that it is distinctly within the

province of the industrial physician to see and treat these minor problems if they are of such nature that the patient can be given relief and returned to finish his day's work in safety. It is also this doctor's responsibility to make as certain as possible that the bellyache is not appendicitis, that the headache is not a brain tumor and that the diarrhea is not a cancer of the rectum. All the patients whose problems seem to demand a bit more than simple first aid are automatically referred to their family doctors for further consideration. The old complaint that the industrial doctor is stealing the bread from the mouth of the family doctor is definitely not justified.

Acutely sick patients, of course, are seen in every industrial clinic. Coronary-artery attacks, renal colic, appendicitis and bleeding or perforated peptic ulcer turn up in industrial practice not infrequently, and the disposition of the case is usually decided on after a telephone conversation with the family doctor. The early observations made in the case, together with simple laboratory work, will usually be of material assistance in making the diagnosis promptly and in saving the patient much time and discomfort. The industrial doctor does not want to take care of these patients, however; he wants to get rid of them, to see them placed in proper hands just as soon as possible.

In addition to the acutely sick persons many men with serious but noncritical conditions come to the industrial clinic. This group includes patients with diabetes, cardiac disease, ulcers, asthma, varicose veins, hemorrhoids, arthritis and a host of other conditions. Some of these men realize that all is not well with them and come to the company doctor seeking advice. They want to know where to go for proper treatment, or for relief. They may be sent to the dispensary by their foremen, who have noticed some indication of failing health; they may even come at the suggestion of the family doctor. Such situations call for a certain amount of diagnostic procedure before one can intelligently advise a man regarding the course to follow. It is important to know whether the problem is serious or trivial, and whether it needs prompt attention or elective treatment. Every large industrial clinic today has x-ray facilities, an electrocardiograph and a laboratory. The use of these diagnostic aids in industry is no attempt to supplant similar facilities elsewhere: it is simply to provide a preliminary survey that, it is hoped, will be of value and help in the ultimate solution of the patient's problem. The thoughtful wharf owner does not object to the placing of channel buoys to guide ships into the harbor.

There is, I should point out, an increasing willingness on the part of large industries to provide this preliminary diagnostic service for more and more people. Periodic physical examinations are required for certain workers in hazardous trades, and the same service is being offered on a voluntary basis to larger and larger groups. In every case the information is available for the family doctor, and frequently it is sent to him whether he wants it or not.

A man came to my office some time ago complaining of a lump in his groin. He was a laborer, foreign-born, and spoke English only with difficulty. Instead of a lump in one groin he had lumps in both — large, egg-sized lymph nodes. The axillary lymph nodes were also involved. He was referred to his family doctor and returned a day or so later with a note from the doctor stating that he was suffering from chronic bronchitis and was able to do his work. I sent him back a second time with firmer instructions. A second note from the doctor admitted the presence of an enlarged inguinal lymph node on one side, and suggested that the man be changed to another job. This time I took no chances and wrote to the doctor urging biopsy and appropriate treatment. My letter was ignored and so was the patient's disease. Some time later the man reappeared with a letter from another doctor. This stated that the man had a generalized rash, occupational in nature, and that he should have a different job. It also stated that night-shift work seemed to be bad for the man. By this time there was massive enlargement of the inguinal, axillary and subclavicular lymph nodes, easily visible from a considerable distance. It might be said that I forced the issue this time, and the patient has received adequate treatment for Hodgkin's disease.

Another man, a leading engineer, came in for a routine physical examination. Both of two urine specimens showed large amounts of sugar. At my suggestion he went to a doctor of his own choice, an eminent internist in this city. Here he was given a clean bill of health and told not to worry. A year later he returned to me saying that he had lost 25 pounds and that he seemed to have developed an uncontrollable thirst. He is now taking insulin. Here I think that both doctors were at fault, — I for feeling that a physician of his eminence could not make a mistake, and he for feeling that anything coming out of an industrial clinic was probably unreliable.

In no situation is the need for co-operation greater than in that of the man returning to work after an illness. Almost every industry, certainly all the large ones, have certain rules and regulations concerning time away from work because of illness. It is common practice for industry to request from the attending physician a note stating that the patient is in his opinion ready to return to his job, and this also provides an opportunity to suggest any limitations or suggestions about the man's work that might be necessary. You would be amazed at the number of notes of this sort which are absolutely insincere and dishonest. No, I am not the only one who has been disgusted with this

situation. Let me quote from Dr. Poole's paper, which touches on the same problem in California:

> These letters are commonly referred to by personnel men and foremen as "82 letters." I frequently hear scornful remarks from plant supervisors who believe that the ethics of the profession can be winked at for small fees and that a physician can be induced to write anything. I must confess that after reading thousands of these letters I have many times shared their opinions.

It is a sordid bit of business and I doubt if even the so-called patient can have much respect for the doctor who would stoop so low. The industrial physician or personnel director must be pardoned, I think, if he refuses to accept as gospel a note that says that a patient has been ill and under a doctor's care, unable to work for two or four or six months because of hypotension or secondary anemia, nervousness or general debility. The pattern is unmistakable, and the authors only too well known.

There is a brighter side to this problem, however, and nothing gives a plant doctor more pleasure than to work together with the family physician in arranging suitable hours and conditions of work for the patient who is recuperating from severe illness. Many physicians fail to remember what a bad enemy the clock is to the patient who is scarcely out of his convalescent stage. Just sitting at a desk until the clock points to five is fatiguing to the person who is "out of training." Not infrequently the industrial doctor must apply the brakes in such a situation, sometimes even insisting that the patient remain away from work entirely for a week or so longer than his own doctor has advised.

Quite a different situation arises when a doctor in all good faith requests that one of his patients be granted a leave of absence from work, or be given a different job, or be changed to a different shift. Frequently the necessity for the recommendation is obvious, and appropriate action will be taken *if this is possible*. Please note those words, "if this is possible." Sometimes it is not possible to carry out the proposed measures. Every industry has definite rules and regulations regarding leaves of absence, for example, and these must be adhered to if the rights of all are to be protected. In addition, nearly every industry has a complicated system of rules regarding job seniority; these rules are usually not of industry's seeking or choice, but they must be followed. Ordinarily it is not possible, for example, to have a short-service man on a night shift displace a longer service employee on the day shift, even though the former's peptic ulcer makes it impossible or inadvisable to continue to work at night. Here is a perfect stalemate, and the poor family doctor doubtless feels that the industry or its doctor is failing to co-operate in the care of the patient. Actually the desire to co-operate is there but successfully blocked by conditions quite beyond the doctor's control.

So far I have talked very glibly about industrial medicine as though all workers had available the same highly organized medical departments as those existing in the large corporations. We all know that this is not so. Actually, many of the workers in Massachusetts have available little or nothing in the way of competent medical supervision. There is no industry so small that it should not and cannot have this medical supervision, but only a handful seem to recognize the fact. The management of a small plant usually believes that it has done everything necessary if it has a nurse and a first-aid room, forgetting that this nurse needs a doctor's supervision. No nurse should be asked or expected to work unless her duties and procedures are outlined and followed by a physician. Simply having a doctor on call for emergencies does not constitute adequate supervision.

This, however, is a situation that cannot be corrected overnight. If a real problem exists and the family doctor wishes to make specific recommendations about a man's work, there are certain procedures that may be employed. First of all, let me join with Dr. Poole in condemning the note that starts off, "To whom it may concern." If no medical supervision for the patient exists at his place of work, one should find out the name of the ultimate boss, the manager, the president or owner, who should be addressed directly either by sealed letter or by telephone. If the patient is entrusted with the note he should be told to see that it gets to the person to whom it is addressed and not to anyone else. It may take an extra day to have the patient find the name of the proper person, but this delay is justified. A letter sent by mail or a telephone call will permit far greater frankness and emphasis than is ever possible in an open note that is handed to the patient.

The average doctor when taking his patient's present and past history usually exhibits a reasonable and healthy skepticism. In considering an occupational history his attitude can only be described as gullible. If a patient says that his job is dusty the doctor more often than not screams "silicosis" before he considers either the patient's symptoms or the nature of the dust. He criticizes a job on the grounds of overfatigue and advises a leave of absence without considering the fact that the man is spending his leisure time building a house or tending a bar. He deplores the heavy work a man does without finding out what that work consists of. An unbelievable number of cases of scabies have been diagnosed as occupational dermatitis, and there appears to be a total inability in the medical profession to discriminate between a toxic hazard and a bad smell. Let me assure you that industry welcomes inquiries on these subjects. It is a pity that it is not more practical for doctors

actually to visit the places where their patients work, to see for themselves what the conditions are, and to find out what the working environment is.

Every patient is affected either directly or indirectly by jobs and wages. Sitting at a desk in a bank is a job just as surely as standing at a lathe or a boring mill. The effect of poor adjustment to a job may be even more damaging to a wife or child than to the worker in question. You, therefore, have a stake in industrial medicine whether you want it or not. Where industrial medicine is practiced well it deserves your support. Where it is practiced poorly and improperly it deserves your constructive criticism more than your condemnation. Where medical supervision of workers is nonexistent your scorn of management that is unwilling to provide it should be followed by your help in showing how it can be obtained. The working man spends forty or more of the one hundred and sixty-eight hours in a week at his job. You cannot disregard this period, and your patient cannot afford to have you do so. Where good industrial medicine exists, cultivate it, get in the habit of using it, learn the ways in which it can help you to get your patients well and keep them that way. Accept the challenge of the missionary work needed to improve industrial medicine and extend its benefits to an ever-increasing number of working men and women, who, incidentally, are your own patients.

FENESTRATION SURGERY FOR DEAFNESS

Present Status

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THE general practitioner is being increasingly plagued by newspaper and magazine publicity describing new technics in medical and surgical therapy. Too often he finds himself confronted with the unpleasant chore of blasting the hopes falsely raised by some garbled or, at best, premature report of a "cure" for high blood pressure, arthritis, asthma, sinusitis, deafness and so forth. The situation takes on the proportions of a real problem, moreover, when the doctor must decide what answer to give a patient who asks about a technic that has really proved to be effective, but only under certain conditions and for certain types of sufferers.

A particularly good example of a therapeutic technic that can tremendously improve a bodily defect and, at the same time, remove its ill effects on the personality is the novovalis fenestration operation. There has been a good deal of publicity about this operation in the decade since Lempert developed the one-stage technic for the cure of deafness due to otosclerosis, and more and more patients are coming to their physicians for information and advice about their chances of benefiting from it.

The first point the physician must determine in deciding whether the patient should consult a surgeon skilled in this technic is the cause of deafness in the particular case with which he is dealing. The fenestration operation is successful only for deafness of otosclerotic origin. Otosclerosis is a histologic lesion in the bone of the inner ear and takes the form of circumscribed, sharply defined, inlaid areas of new bone formation of unknown etiology and microscopically somewhat like Paget's disease or osteitis fibrosa. In otosclerosis the piling up of new bone formation is usually about the foot plate of the stapes, and the deafness progresses as the fixation of the stapes increases. The fenestration technic consists in making a new fenestra in the inner ear so that sound waves can by-pass the obstructed middle-ear circuit.

The general practitioner can make at least a tentative diagnosis of otosclerosis on the basis of history and symptomatology. The patient usually gives a history of bilateral deafness beginning in adolescence or early adult life and, as a rule, becoming progressively worse. Although in some cases deafness does not develop beyond the point where practical hearing is possible, most patients suffer progressive impairment to a degree where hearing loss is incapacitating. Many of them ultimately show nerve degeneration. There may be found a past history of acute otitis media, but this finding does not preclude a window operation if the eardrum membrane is intact. A chronic suppuration of the middle ear, on the other hand, is a contraindication.

As part of his general information about this disease, the physician may find it helpful to know that a hereditary factor has been found in 53 per cent of cases. Also, about six times as many women as men have otosclerosis, and in about half the female patients impairment of hearing increases during pregnancy.

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It is characteristic of the otosclerotic patient to hear well over the telephone and in noisy places such as a subway or railroad train. Good hearing over the telephone, it is true, may be found in chronic catarrhal or chronic adhesive deafness, but here one can elicit a history of nasal allergy or chronic upper respiratory infections and earaches with or without discharge. Examination provides another differentiating point: in otosclerosis the eardrum is normal, without perforation or discharge, and gray or pink in color unless complicated by an isolated attack of otitis media. In the other type of deafness mentioned, the eardrum may be thickened, atrophic, scarred and possibly perforated anteriorly.

Tuning-fork tests will show the otosclerotic patient to have prolonged bone conduction and diminished air conduction. He characteristically hears well with a hearing aid of either the air-conduction or bone-conduction type. In fact, this type of patient does not have to rely solely on the fenestration operation for help; even if he proves eligible for it by all the various criteria used by the surgeon in advising operation he can always fall back on a hearing aid instead of submitting to surgery. The decision about undergoing surgery actually rests with him, but many of these patients are not willing to use a mechanical device despite its effectiveness.

Certain other factors must be taken into consideration in judging a patient's chances of benefiting from a fenestration operation. One of them is age. Persons between eighteen and fifty are the most eligible although younger and older patients have been operated upon with good results. Another factor is emotional stability. Since not every operation can be guaranteed to be an unqualified success, and the aftertreatment, in every case, is necessary and since a few patients occasionally develop postoperative vertigo, the emotionally unstable person is a poor psychologic risk.

When a patient is referred to an otologist for study preliminary to possible fenestration surgery, a number of devices designed to gauge cochlear-nerve function help the surgeon make his decision. He will use air and bone audiograms, tuning-fork tests, the speaking tube and word tests played on a recording machine.

Although the fenestration does not give perfect hearing, it does make possible practical hearing that enables the patient to carry on a conversation, attend lectures or church and otherwise live a normal life. For properly selected patients, the chance of bringing the hearing to a permanently serviceable level is about 50 per cent. By permanent is meant a period longer than two years, after which period no patients with successful cases have lost their hearing. I performed my permanently successful cases of oldest standing in December, 1941, and these patients have lost none of their hearing gains. Of 64 operations performed between December, 1941, and April, 1946, 31 were successful — or 48.5 per cent.

Patients who have undergone successful operations say that their hearing has none of the distortion produced by the hearing aids they formerly had recourse to and also that they can be more selective in their hearing. In other words, the hearing made possible by the fenestration operation is more satisfactory than that effected by a hearing aid because it is more natural.

What to me is the most striking effect produced by a successful fenestration operation is the extraordinary change for the better in the patient's personality. The self-conscious, dejected, hypersensitive person with inferiority feelings living a life circumscribed by the limitations put on his activities by deafness emerges from this operation a more self-confident, happy and better adjusted man or woman possessed of an energy, enthusiasm and joy in living that is tremendously rewarding to see.

MEDICAL PROGRESS

RENAL DISEASE*

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WE ASK the reader's indulgence for some liberties in the selection and presentation of recent developments in renal disease. The literature on the kidney is too large to permit any complete description in these few pages. We have therefore chosen a few subjects of current interest for discussion. These include some studies of the earlier stages of glomerular nephritis and a glimpse of the gradually evolving cardiovascular-renal relations. The curious effects of large doses of vitamin D on the kidney are mentioned. The acute renal tubular injury that accompanies many types of bodily injury is now recognized as one of the commonest and most important forms of renal disease. Its etiology is discussed and related to the novel studies of Trueta on the renal circulation. Finally, some new methods for the treatment of acute renal insufficiency are described.

GLOMERULAR NEPHRITIS

Two important new books on nephritis have appeared this year. In his scholarly work on Bright's disease, Christian[1] presents a well organized, detailed description of the present state of knowledge of renal disease. The author follows his well known system of classification of renal disease. Clinical descriptions include numerous case histories, charts, and pathological descriptions. A large bibliography offers opportunities for further study.

Addis[2] has published a thoughtful, personal account of his studies on glomerular nephritis, and of much related experimental work. His book contains a detailed consideration of the clinical features and laboratory evidences of glomerular nephritis, as well as a unique presentation of treatment as applied to an individual patient. In contrast to the usual textbook, the author probes with obvious relish into vast areas of present ignorance about the causation and treatment of nephritis. A number of current physiologic and therapeutic principles emerge somewhat battered from the encounter.

A large part of Addis's book is devoted to the argument for a diet of minimal protein content throughout the course of glomerular nephritis. "Renal work" in secreting urine consists largely in concentrating urea from a low level in the blood to a high level in the urine. Of course, the kidney does much work of other sorts, but the work imposed by a high-protein diet has been repeatedly shown experimentally to be injurious to a damaged kidney. The normal or damaged kidney hypertrophies when the dietary protein is increased. However, when the capacity for urea excretion is exceeded by dietary nitrogen, signs of further renal injury appear in the form of protein, red blood cells and casts in the urine, together with a rising blood pressure and a progressive anemia. These animals die in uremia, which is readily avoidable by the use of a low-protein diet. The same general principle may apply to patients with limited renal function and perhaps to patients who have had an attack of acute glomerular nephritis.

Addis also emphasizes an adequate fluid intake at all times. This serves two purposes: the minimizing of renal work, and the prevention of protein precipitation in the renal tubules. He regards dehydration as dangerous to the patient with proteinuria, a thought to consider before ordering a test of urinary concentrating power. A daily intake sufficient to yield 2 or 3 liters of urine is considered adequate. Above these levels, increases in the fluid intake become less efficient as well as difficult to maintain.

Acute Stage

The etiology of acute nephritis is known in general outline, but the specific mechanism remains obscure. The occurrence of several cases in the same family has suggested a "constitutional" predisposition. Addis reports 4 cases of nephritis occurring in only 1 of identical twins. In 1 of these cases the children lived under apparently identical conditions, sleeping in the same room, and each was recovering from a mild attack of scarlet fever when 1 of the twins developed acute nephritis. An essential, nonhereditary factor is strongly suggested by such observations.

Cardozo[3] has recently described an increased volume of the blood in acute nephritis. Addis had suggested that the sudden development of mild anemia and hypoproteinemia, and their reversion to normal levels with diuresis, were due to changes in plasma volume. We have examined this point

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in some detail.[4] During the initial stage, with or without oliguria, the excretion of sodium is greatly depressed. If gastrointestinal symptoms do not block the intake of water and salt, edema develops rapidly. At this stage, the plasma volume is usually increased far above the expected figure. The venous pressure is frequently as high as in cardiac failure, and yet symptoms of failure are not necessarily present. With the onset of diuresis, all these changes may be reversed with astonishing speed. Sodium and water pour out through the kidneys, edema disappears, the plasma volume contracts rapidly, and the plasma protein concentration mounts, sometimes overshooting the mark to a level of 9 or 10 gm. per 100 cc. The proportion of albumin is usually unchanged during diuresis, suggesting that there has been a simple concentration of the plasma proteins. When the venous pressure has been elevated, it falls as the edema is eliminated. These findings suggest that retention of salt and water accounts for many of the changes observed in acute nephritis, although doubtless other factors play important roles.

The excellent prognosis in acute nephritis has been emphasized by recent reports.[5–7] Treatment is currently directed at minimizing the physiologic disturbances as they appear. The recently developed antihistaminic drugs suggest the possibility of blocking some effects of the hypothetical antigen-antibody reaction responsible for glomerular nephritis, but only preliminary reports[8] of their successful use have been forthcoming. Penicillin has been very useful in controlling the preliminary infection, and preliminary reports indicate that it may reduce the severity of the ensuing nephritis.[9]

Nephrotic Stage

A comprehensive review of the nephrotic syndrome by Bradley and Tyson[10] recently appeared. The following discussion covers only certain new information in its relation to the nephrotic syndrome.

Many students of the nephrotic syndrome believe that hypoproteinemia can no longer be considered the sole cause of edema.[2, 10, 11] Perhaps the most revealing data came from the studies of treatment of the nephrotic stage with concentrated human serum albumin.[12–15] Albumin has proved to be a safe and frequently effective diuretic, but in most cases, the serum protein concentration is not increased above so-called "critical levels" for edema. The increased circulating albumin draws in fluid to produce a large increase in the plasma volume, clearly demonstrating the Starling effect.[16] When fluid is mobilized from the periphery, however, the excess fluid is not necessarily excreted. The patient may be left with the anomalous combination of a normal total amount of albumin and globulins circulating in his blood, but with double the normal plasma volume and with only half the normal protein concentration. This situation throws the responsibility for the hydremia and edema directly on the kidney's failure to excrete sodium and water.[17]

The specific difficulty in sodium excretion in the nephrotic syndrome is well recognized. An attempt to reproduce this defect by the classic methods of protein depletion in dogs has been made.[4] Acute plasmapheresis to plasma protein levels around 2.5 gm. per 100 cc. does not appreciably impair the dog's ability to excrete sodium or water. Chronic protein depletion causes some diminution in excretory function, involving sodium and water to a limited degree. In general, the results do not resemble those found in the nephrotic syndrome, and one is forced to assume that the nephrotic patient's difficulty in the excretion of sodium and water is not due to hypoproteinemia per se. This conclusion is supported by the observation of spontaneous diuresis in nephrosis without a preceding increase in the plasma protein concentration. The depression of sodium excretion in the edematous nephrotic patient may be related to the failure of sodium excretion in acute glomerular nephritis, and may represent a response to this form of renal injury.

Chemical changes preceding a diuresis in a cyclic form of nephrosis have recently been described by Rytand.[18] A rise in urinary alkalinity was the first sign of impending diuresis. Excretion of water preceded the release of sodium and chloride into the urine. We have observed a group of patients with nephrosis who showed a similar lag in the appearance of sodium in the urine, with a corresponding rise in the serum sodium concentration. Excretion of water without sodium may also occur for brief periods at the beginning of albumin treatment in severe nephrosis.[4]

The various forms of treatment of nephrotic edema are critically examined by Thorn[19] in a recent review. The basic measure is the low-sodium diet, abetted by acid-ash diet, acidifying diuretics or potassium salts if renal function permits. If signs of circulatory failure appear, digitalis is indicated. The mercurial diuretics are avoided as potentially dangerous. If renal function is adequate, urea may be given in large amounts by mouth to eliminate fluid from the body, but the fluid intake must be restricted. Amino acids or a high-protein diet is helpful if there has been a prolonged dietary deficit in protein or if the physician wishes to take advantage of the resulting high output of urea, but it requires careful planning to keep the sodium intake low when much protein or amino acids are given. Concentrated human serum albumin for intravenous use has advantages over plasma in its lower sodium content and its freedom from risk of homologous serum jaundice.* Other

*Concentrated human serum albumin is now scarce and expensive, and one can only hope that voluntary blood donation through the American Red Cross and local programs will furnish adequate supplies of this valuable agent.

protein products are more readily available than albumin, but there are some reservations concerning their use. Southey's tubes remain a very effective means of removing accumulated edema without appreciable risk if careful sterile technic and penicillin therapy are used to eliminate infection. The induction of measles in nonimmune children may initiate a diuresis.[20]

Varieties of the Nephrotic Syndrome

To the difficult differentiation of lipoid nephrosis from the nephrotic stage of glomerular nephritis, Addis[2] adds a third possible choice: a benign, cyclic form of nephrosis. Occurring at any age, a suddenly developing proteinuria is followed by most of the features of the nephrotic syndrome, which may subsequently disappear completely. Recurrences and remissions are seen. Death may rarely occur in the edematous stage, and a few post-mortem studies have shown no glomerulitis. The urinary sediment is not distinctive until after prolonged proteinuria. The urine may return to normal during remission, a finding that Addis regards as incompatible with a diagnosis of glomerular nephritis.

Rytand[18] has observed a cyclic nephrosis following bee sting. Tridione has been implicated as a cause of the nephrotic syndrome.[21] Early syphilis[22] and amyloidosis[23, 24] as causes of nephrosis are the subject of recent reviews.

Cardiovascular-Renal Relations

Renal Failure

The kidney occupies a strategic position in the regulation of the fluid and electrolytes on which the cardiovascular system depends for its normal function. Hypotension and collapse may occur in the "salt-losing nephritis," as well as in Addison's disease, when excessive amounts of sodium and water are lost in the urine.[25] In acute nephritis, the retention of sodium and water is associated with edema, an increased venous pressure and a dilated heart, as well as hypertension. Although the terminal stage of nephritis usually includes hypertension, cardiac embarrassment and retinal-artery disease, the patient with "salt-losing nephritis" usually escapes these complications until the last stages of his illness, when edema may also appear.[25] These observations strongly suggest that the kidney's handling of salt and water may affect the cardiovascular system.

Cardiac Failure

Studies of cardiac failure indicate that the kidney is equally sensitive to failure of its normal cardiovascular support. Warren and Stead[26] have shown that in congestive heart failure, the kidneys fail to excrete salt and water in the normal manner, with resultant edema. They have further demonstrated that this salt retention is due to diminished cardiac output, and not to venous engorgement of the kidneys or to increased venous pressure, as has long been the accepted view. They point out that the retention of salt and water takes place before there is any demonstrable increase in venous pressure. Merrill[27] states that the decreased volume of glomerular filtrate, combined with normal reabsorption of salt by the tubules, leads to salt retention. Mokotoff, Ross and Leiter[28] have also emphasized the relative constancy of the tubular reabsorptive mechanism for sodium despite variations in glomerular filtration rate. The acute sensitivity of the kidney to shock is described below. It seems quite possible that there is a common, central, regulatory mechanism that is stimulated to conserve sodium and water in an effort to sustain blood volume and cardiac output during cardiovascular emergencies.[29–31]

Hypertension

The renal handling of sodium and water may play a role in "essential" hypertension. Perera and Blood[31] believe that hypertensive patients excrete sodium with some difficulty, owing to abnormal activity of the adrenal cortex. This is based on experiments with a comparative study of normal and hypertensive patients from whose diet salt was withdrawn for twenty-four hours. There was weight loss and diuresis in the control group, but these changes were not observed in the hypertensive patients. Landis and Abrams[32] report that hypertensive rats have an aversion for sodium chloride and bicarbonate, and when desoxycorticosterone is given this aversion is increased. These hypertensive rats did not show any particular appetite for ions supposed to reduce hypertension, such as ammonium, magnesium, thiocyanate and nitrite. These findings support an important role attributed to sodium chloride and the adrenal cortex by Selye,[33] in his general adaptation syndrome and in other observations by Selye and Stone.[34] These developments furnish some foundation for the use of low-salt diets in the treatment of hypertension.[35, 36] It seems likely that the success of Kempner's[36] rice diet is dependent on its low-salt and low-protein content. In this connection, it is interesting to note further observations by Selye's group[37] in which they have shown that the nephrosclerosis induced by the injection of anterior pituitary substance in rats is accompanied by hypertension, and that a low-casein diet is effective in preventing both. They also observed a significant increase in the weight and size of the adrenal glands in animals fed the high-protein diet.

The role of the kidney in the causation of hypertension is still unsettled. It seems clear that renal ischemia can cause hypertension,[38–40] but in the majority of patients, hypertension is not associated with a demonstrable, primary, renal lesion.[41, 42] There is still a real problem in the selection of the

hypertensive patients with unilateral renal disease for nephrectomy. In a recent review of the subject, Smith[43] has analyzed 242 reported cases in which nephrectomy was performed. In assessing the value of operation, only 47 of these met the criteria, which included a clear demonstration of, first, pre-existing hypertension, secondly, reduction of blood pressure to normal levels (140 systolic, 90 diastolic or below) and, thirdly, persistence of blood pressure at this level for a year or longer. Smith considered the operation successful in 19 per cent of the cases. Sabin[44] has reviewed 106 cases in which nephrectomy was performed for hypertension associated with unilateral renal disease. Pyelonephritis was the commonest offending pathologic lesion (45 per cent of the total), as in Smith's series. In Sabin's group, the blood pressure became normal in 51 patients, reduced in 23 and unchanged in 26 — a more successful result than that in the cases reported by Smith, largely because of variations in criteria. Landley and Platt[45] have evaluated a similar group of patients. Smith concludes that the advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure. If bilateral disease is present (and it usually is present in advanced hypertension), as a result of the hypertensive process itself, nephrectomy may shorten life by removing an important fraction of total available renal function.

Renal Disease in Diabetes Mellitus

Robbins[46] discusses a group of conditions of frequent occurrence in diabetes, including glycogen nephrosis, nephrosclerosis, intercapillary glomerulosclerosis, pyelonephritis and necrotizing papillitis.

Glycogen nephrosis is a benign renal change limited to diabetic patients and those with von Gierke's disease (glycogenosis). In general, the presence of this finding at autopsy is dependent upon terminal control of the diabetes and not so much on the severity of the diabetes.

"Benign nephrosclerosis" is a frequent finding especially in older patients with hypertension. It occurs in a relatively younger age group and runs a more serious course in patients with diabetes.

Intercapillary glomerulosclerosis as defined by Robbins occurs only in diabetes, although closely allied pathological changes are found in nondiabetic persons. Kimmelstiel and Wilson's[47] cases were examples of the nodular type, which probably does not occur without diabetes.[48] A similar glomerular lesion occurring in diabetes mellitus is the diffuse type, which bears a close resemblance to changes seen in chronic glomerulonephritis and in nephrosclerosis.

Most recent observers agree that it is not easy to make the diagnosis clinically.[46, 48–50] Long duration of diabetes predisposes to the renal change, although the diabetes need not be severe. Hypertension is of little diagnostic significance in an older diabetic patient. Albuminuria is also a common finding, but profuse albuminuria indicates a probable glomerular lesion. Hypoproteinemia and edema favor intercapillary glomerulosclerosis, but occur in only a small proportion of cases. Slowly developing renal insufficiency and a mixed vascular and diabetic retinopathy may be present. Robbins[46] suggests that a correct diagnosis can be made clinically in 60 per cent of the cases. In a recent report, Adams[50] discusses 5 interesting cases in young diabetic patients that fit the clinical criteria, but the pathologic lesions were found to be a combined inflammation and vascular hyaline degeneration.

Acute pyelonephritis is four and a half times more common a cause of death in diabetic than in nondiabetic patients; and 1 in 5 diabetic patients at autopsy shows some acute pyelonephritis.

Necrotizing renal papillitis is a peculiar form of pyelonephritis with massive necrosis of the renal pyramids, frequently involving all pyramids of both kidneys. Edmondson, Martin and Evans,[51] in a series of 859 diabetic patients, discovered 29 patients with renal papillitis, an incidence of 3.4 per cent. The organisms most commonly noted were *Escherichia coli* and *Staphylococcus aureus*, but *Mycobacterium tuberculosis* and actinomyces were each found once. In the same series of 32,000 autopsies, these workers observed pyelonephritis in 1023 nondiabetic patients, of whom 21 had lesions characteristic of papillary necrosis. In 20 of these it was a complication of urinary-tract obstruction. Robbins, Mallory and Kinney[52] discussed 26 cases; 19 of the patients had diabetes, and all except 1 of the seven nondiabetic patients had an associated urinary-tract obstruction. Mallory, Crane and Edwards[53] have produced similar lesions in rabbits by ligating one ureter and injecting suitable pathogenic organisms into a vein. The lesions appeared only in the obstructed kidney.

The symptoms of necrotizing renal papillitis may be acute, with sudden onset of prostration, septic type of fever, tachycardia, leukocytosis, pyuria, oliguria, azotemia and a fulminating course ending in death within three or four days. In other cases, a subacute, protracted type appears, characterized by weeks or months of purulent pyelonephritis, with a terminal exacerbation resembling the acute form of necrotizing papillitis. Richfield[54] and Stevens et al.[55] have reported cases, the latter group including an interesting review of the subject.

Edmondson and his co-workers[51] suggest that criteria for diagnosis of necrotizing papillitis in diabetes should include hematuria, renal colic, sudden appearance or aggravation of pyelonephritis and signs of sepsis or unexplained coma. Earlier, Mellgren and Redell[56] also described colic, explained by obstruction of the ureter by a sloughed papilla.

Characteristic roentgenographic signs have been reported by Alken,[67] who describes a cavity-like enlargement and deformity of the calyxes in the pyelogram, resembling the findings in some types of renal tuberculosis. Edmondson[51] has more recently emphasized this point.

The early recognition of this serious complication, and the prompt institution of therapy may give the patient some chance of recovery.

Irradiated Sterol Poisoning

This type of renal injury must be considered in any cases of uremia of obscure origin, and a history of joint pains and vitamin treatment should be sought. The widespread use of large doses of potent irradiated sterols for arthritis has made hypercalcemic renal insufficiency no longer a rarity.[58, 59] There is a wide individual variation in susceptibility to these products. Anorexia, nausea, abdominal pain and muscular weakness may give warning of a rising serum calcium. Prolonged hypercalcemia may lead to metastatic calcification of many tissues. Walsh and Howard[60] have recently described glistening deposits in the conjunctiva and cornea, visible under the slit-lamp, developing soon after a rise of the serum calcium.

Polyuria is often the first symptom of renal involvement. The urine is usually dilute and may contain no trace of albumin. Microscopical examination of urine may show casts containing black granules, which dissolve in acid. The finding of a grossly elevated blood urea may come as a surprise with such a benign urinalysis. If Sulkowitch's[61] simple test is applied to the urine, the hypercalciuria is at once apparent. The mystery is quickly solved when the patient is questioned specifically about vitamin D ingestion. Hyperparathyroidism must be considered if no history of medication can be obtained, and may raise a difficult diagnostic problem, since the serum calcium subsides very slowly in some patients when vitamin D is withdrawn. The normal condition of the bones and the high level of serum phosphate after vitamin D administration may be helpful.

Rare Renal Lesions

Interesting cases of renal involvement by polycystic disease,[62–64] periarteritis nodosa,[65] sarcoidosis[66] and sickle-cell disease[67] have been reported.

Acute Renal-Tubule Injury

Lower-nephron nephrosis is the term designated by Lucké[68] to describe the renal lesions produced by a wide variety of traumatizing conditions that have in common the main feature of shock. Harkins[69] has listed more than 30 causes of shock, including trauma, burns, freezing, vascular occlusion, intestinal strangulation, bile peritonitis, visceral perforation, toxic drugs, venoms, anaphylaxis, transfusion reactions and fulminating infections. It is possible for renal lesions to develop secondarily to any one of these. Indeed, numerous recent reports[70–74] indicate the diversity of the etiologic factors, including many of those listed above.

Harman[71] has reviewed 1065 autopsies of battle casualties and found evidences of lower-nephron nephrosis in 152, or 14.2 per cent. Of these, 70 patients had died of renal insufficiency. The exciting causes included vascular damage, muscle trauma, crush, transfusion reaction, hemorrhage, burns, gas gangrene and shock. He also observed that the administration of sulfonamides had not increased the incidence or severity of the nephrosis.

Tagnon and his co-workers[72] have reviewed the situation regarding burns. They report 450 patients who lived more than two weeks after the burn and showed no evidence of lasting kidney dysfunction. On the other hand, of 35 patients who died less than two weeks after the burn, 14 had definite clinical and pathological evidence of renal injury. Martineau and Hartman,[73] in a combined experimental and clinical study of burns, conclude there is a close relation between the "burn" kidney and the renal findings of other conditions characterized by intravascular hemolysis.

In relation to shock from trauma and burns, Fox and Baer[75] have correlated death with extrusion of considerable potassium from injured cells and their acquisition of an equivalent amount of sodium. They believe that this exchange results in swelling of uninjured tissue cells throughout the body, leading to additional reduction in extracellular fluid and blood volumes.

Sanderson[74] has reported 4 cases of renal insufficiency following abdominal catastrophe in which he believed that dehydration played a dominant role.

Corcoran, Taylor and Page[76] and, more recently, Kugel[77] have used the term "acute toxic nephrosis" to apply to cases that are primarily the result of poisoning or from hemolytic transfusion reaction. Many such cases have been reported. Bock et al.[78] have reported a case due to sulfadiazine; Woods[79] and Kugel[77] cases due to carbon tetrachloride, Anderson[80] a case of renal damage resulting from sensitivity to neoarsphenamine, and Corcoran, Taylor and Page[81] cases of vitamin D intoxication and mercuric bichloride poisoning.

The renal lesions occur in a similar region in all these cases, with selective tubular damage to the ascending loops of Henle and the distal tubules. The glomeruli and proximal tubules are only indirectly affected. These pathological findings have been described by Lucké,[68] Mallory,[82] Bywaters[83] and others. Woods[79] has remarked on the similarity of the renal changes in the crush syndrome and carbon tetrachloride poisoning.

The mechanism of the production of this renal injury has been the subject of much experimental

work. Corcoran and Page[84] showed that shock and early hypotension from bleeding resulted in renal vasoconstriction, and that subsequent raising of the arterial blood pressure and blood volume by transfusion failed to restore the indirectly determined renal blood flow to more than 50 per cent of normal. In an earlier work, Page[85] suggested that the vasoconstrictive ischemia is of humoral origin. In this connection, Little, Green and Hawkins,[86] in crossed-transfusion experiments with shocked and normal dogs, were unable to observe any impairment in urine formation that could be attributed to the operation of a humoral factor and concluded that it was probably due to a lowering of the mean arterial pressure together with homeostatically induced renal vasoconstriction.

Corcoran and Page[84] summarize the sequence of events as follows: vasoconstrictive renal ischemia occurs with onset of shock or injury and more or less myoglobin diffuses into the blood from the crushed area and is filtered into the renal tubules; pigmentary precipitation may then occur and is facilitated by the presence of a urine that is acid and of small volume. Bywaters[82] and Mallory[82] agree that the formation of precipitated material in the tubules may contribute to the progress of the lesions once they are initiated by renal ischemia, though they do not believe that mechanical obstruction is the cause of renal failure. Lucké[68] states that in many of his cases he found few pigment casts and points out that in the anuria of shock the urine is of low specific gravity and small volume, indicating a more general renal lesion. In this connection, Yuile, Gold and Hinds[87] conclude that the precipitation of hemoglobin in the renal tubules is primarily dependent on antecedent damage to the tubules and not on the acidity or alkalinity of the urine or the amount of hemoglobin in the blood.

The similarity of the lesions produced by nephrotoxic substances and shock has led Lucké to suggest that the cause of renal insufficiency is the same in both conditions. It is generally agreed that renal ischemia is the first step.[88, 89]

Neural Control of the Renal Circulation

An important new description of the renal circulation promises to shed light on some of these obscure problems in renal dysfunction. Trueta et al.[90] present convincing evidence of a dual circulation to the kidney under the control of the autonomic nervous system. The work began with arteriograms of the hind limbs of rabbits after a simulated crushing injury. Arterial spasm was demonstrated not only at the level of the injury but also extending proximally and sometimes into the opposite limb. The renal arteries were found to be singularly sensitive to this reflex spasm, which persisted for hours after the injury. The blood pressure did not fall enough to account for such a compensatory vasoconstriction. It was found that stimulation of afferent sciatic-nerve fibers, of efferent splanchnic-nerve components or of fibers about the renal artery caused renal-artery spasm. Other effective stimuli were rapid hemorrhage, large doses of epinephine or pitressin and the injection of staphylococcus toxin.

In an excellent series of radiographs and pigment injections, Trueta and his co-workers demonstrated a striking diversion of intrarenal blood flow from the cortex to the medulla of the kidney during the various procedures used to excite the renal-artery spasm. The blanching of the cortex was observed directly on the exposed kidney. The renal blood flow did not stop, but the renal vein sometimes took on a bright-red color and a pulsatile flow. The rapid renal-circulation time as measured by dyes suggested that an actual shunt of blood through the medullary circuit might occur.

The arterial spasm affecting the outer two thirds of the cortex failed to impair the circulation to the innermost glomeruli. These juxtamedullary glomeruli were dilated, and supplied the first link in the medullary shunt, which then continued through the vasa recta deep into the medulla. The vasa recta mingled freely with the long loops of Henle arising from the deeper glomeruli. It is suggested that this is an ideal site for water reabsorption, and that the diversion of circulation to the medulla may lead to oliguria or even to anuria.

Most of these experiments were done in rabbits, which are known to have a very labile renal circulation, but the work has now been extended to several other mammals and doubtless will soon be tested in man. Normal men have a very steady rate of glomerular filtration, but there is evidence that disease may modify this picture. In particular, hemorrhagic shock is known to affect renal clearances out of all proportion to the fall in blood pressure.[88] In dogs, the clearance of para-amino hippuric acid, which usually measures renal blood flow, may be depressed well below the actual renal flow for prolonged periods, even after blood transfusion has increased the blood pressure to normal levels.[84] Collateral evidence[84, 88, 89] points strongly to a redistribution of circulation through the kidney in hemorrhagic shock and may indicate the presence in man of a shunt such as Trueta and his co-workers have demonstrated. It also seems likely that reflex and hysterical anuria may depend on renal vasospasm. The importance of ischemia of the renal cortex in the development of the crush syndrome and allied states has already been pointed out.

Diseased kidneys may contain juxtamedullary glomeruli that have degenerated into little more than direct passages for the escape of blood from the arteries to the vasa recta. Trueta and his co-workers suggest that these are produced in some cases by repeated reflex diversion of the blood through the medullary circuit. If such changes could follow emotional stress, a possible explana-

tion for the development of cortical ischemia and of a chronic hypertension might be imagined. Endless fields for speculation on the possible effects of the reflex control of the renal circulation are opened up, and further experimental studies are eagerly awaited.

Treatment of Acute Renal Insufficiency

Therapy is considered in three stages: immediate, specific treatment to minimize damage; regulation of fluid and electrolyte balance; and dialyzing procedures to reduce azotemia.

Initial Measures

The first aim of therapy is to limit the extent of damage as far as possible. The first measure is replacement of lost blood and fluid in cases of severe shock, and pressure bandaging of the affected part before removal of the tourniquet in cases of trauma.[84] It is during this period of the first few hours that renal ischemia is present and renal blood flow and renal function are reduced.[88, 89] Dogs can tolerate complete renal-artery occlusion for as long as two or three hours without irreversible damage.[91, 92] The timing of blood replacement is of utmost importance to the ultimate outcome, since in the earliest stages serious renal injury may be avoided.

In the nephrotoxic cases, the immediate exclusion or neutralization of the offending agent is of prime importance. Alkalinization of the urine is valuable in the prevention of renal injury by sulfonamides, and may be useful in transfusion reaction, although there is still difference of opinion about the efficacy of this. Thus, Flink[93] reports that in dogs the excretion of hemoglobin proceeds at about the same rate and produces approximately the same renal damage whether the urine is acid or alkaline. On the other hand, Fox et al.,[94] Corcoran and Page[84] and others recommend the alkalinization of the urine after transfusion reactions. Clinically, the use of alkali appears of limited value unless given early and in adequate dosage.

BAL[95] may be life saving in mercuric bichloride poisoning, but prompt institution of therapy is important. Most patients have recovered despite very large doses of mercuric chloride, when BAL was given in adequate dosage within four or five hours after poisoning. When treatment is delayed for six hours, the effectiveness of BAL is much less striking. Sodium formaldehyde sulfoxylate is recommended for lavage of the stomach, to inactivate unabsorbed mercuric chloride.

Fluid and Electrolyte Balance

When a patient is found to be passing no urine, and when obstruction of the urinary tract has been ruled out, there is a natural impulse to force fluids to "open up the kidneys." Dehydration and shock are strong indications for immediate parenteral therapy, but often the treatment is continued too long and too vigorously when no urine is excreted. After some days of heavy intravenous fluid therapy, the patient is edematous, circulatory failure may be imminent, and frequently the concentration of sodium and chloride in the plasma is depressed to dangerous levels.

The error in treatment arises from failure to recognize the elementary fact that *the anuric patient cannot excrete water* except in very limited amounts in breath, sweat and stools. There is every reason to establish a normal circulation and state of hydration, but there are equally cogent reasons for not exceeding the normal range of fluid volume. Another liability of the anuric patient is his inability to excrete potassium, which slowly increases in concentration in the plasma until dangerous or fatal levels are reached.

Hope must not be lost even when the outlook seems darkest, for diuresis may begin at any time if the patient is kept in good condition. Since the renal injury is usually self-limited, a remarkable restoration of function occurs if the patient can be tided over the critical period.

Thorn[19] has outlined a program to be followed during this phase:

> The careful restriction of fluids so that no gain in body weight is observed during the period of anuria. In most patients 1000 to 1500 cc. of fluid for twenty-four hours is adequate in the absence of fever or fluid loss from vomiting, diarrhea or other causes.
>
> The provision of as high a caloric intake as possible during the early stage of anorexia and vomiting; 15 per cent glucose solution as an infusion will reduce endogenous protein breakdown.
>
> The use of small quantities of plasma (½ unit) or normal human serum albumin (10 to 15 gm. daily) in the glucose solution to maintain blood volume and to prevent to some extent excessive fluid dissipation into the extracellular spaces. Intravenous albumin and plasma may reduce endogenous nitrogen breakdown somewhat.
>
> Digitalization at the first evidence of cardiac enlargement or pulmonary congestion.

The quantity of sodium chloride to be given each day should be planned to keep a normal concentration of these electrolytes in the plasma. Kugel[77] suggests 5 or 6 gm. per day to supply the approximate amount required daily by the normal person and that this amount be increased or decreased according to the state of hydration. He also points out that marked tissue weight loss occurring during this period may release a large volume of intracellular fluid, which aggravates the edema.

By this conservative routine, spontaneous diuresis may be effected on the tenth to the twelfth day in many cases, especially the less severe ones, and the

patients will go on to recover. Thorn[19] and Kugel[77] have reported cases in which such recoveries have taken place.

In the severe cases such an outcome may occur, but resort to more radical means of correcting the azotemia and electrolyte unbalance may become necessary. These procedures are discussed below.

Phase of Diuresis

Burwell, Kinney and Finch[96] point out that the second peak in the mortality rate in cases of intravascular hemolytic crises occurs on the tenth day regardless of the fact that many of the patients had shown a spontaneous diuresis at that time. Thorn[19] suggests that this is related to the development of hypochloremia and subsequent dehydration at a time when the renal lesion is actually improving but normal function has not been completely established. Large amounts of sodium chloride and water may be required during this period, or, in rare cases, water without salt must be given.[97] The amount can only be determined by close examination of the serum chloride and bicarbonate levels until the kidney has recovered its normal regulatory functions.

Artificial Kidney

With the increased incidence and recognition of lower-nephron nephrosis and toxic nephrosis during recent years, there has been a strong impetus to further the clinical application of the original work done by Abel, Rowntree and Turner[98] in the removal of diffusible substances from the blood by dialysis. Several methods have been evolved by different investigators and applied clinically with varying degrees of success.

Kolff,[99] Alwall[100] and Murray[101] have developed "artificial kidneys" and applied them successfully in many cases of renal failure. They differ in some respects, but all use cellophane as the membrane to remove diffusible crystalloids from the blood to the exterior as well as to maintain the normal concentration of the essential components of the blood.

Kolff[102] has recently reviewed some of his results. Of the first 15 patients on whom the artificial kidney was used, 14 died, and of the next 16, 10 died. These apparently disastrous results were due to the high percentage of chronic renal disease, in which any improvement could be only temporary. On the other hand, he cited several cases of successful treatment of uremia in patients with acute glomerulonephritis and mercuric bichloride poisoning.

Alwall[103] claims that his dialyser is superior to that of Kolff and lists advantages to support his view: the apparatus is small; all the cellophane is in contact with saline solution; the blood does not have to pass the rotation cylinder; arterial pressure is the driving force lessening the incidence of hemolysis; there is less risk of coagulation; heparin dosage is reduced, and there is therefore less tendency to hemorrhage; and the blood pressure does not fall, and therefore there is no shock. Certainly, the reduction of hemorrhage and shock would be important advances. Alwall has reported successful cases in which his apparatus was used, both experimentally and clinically.

Murray[101] has had good results with his artificial kidney in experimental work. One of his clinical cases with renal shutdown secondary to an induced abortion is particularly enlightening. Repeated use of the artificial kidney kept the patient alive until the kidneys were able to secrete urine, and progressive recovery ensued. As much as 6.6 gm. of nonprotein nitrogen was removed with a single period of dialysis.

In contrast to these generally successful reports, Muirhead and Vanatta[104] have tested the artificial kidney experimentally on dogs, and, after disastrous results, concluded that in its present form it is not ready for clinical application.

At present, the artificial kidney appears to be a promising therapeutic instrument for treatment of acute renal insufficiency, but its use is not without risk. It requires a trained medical and technical team for effective performance.

Peritoneal Dialysis

Suggested many years ago by Ganter,[105] peritoneal dialysis has recently been reintroduced by Seligman, Frank and Fine[106, 107] in the treatment of acute renal failure. Fine, Frank and Seligman[107] Goodyear and Beard[108] and Muirhead et al.,[109] to mention a few, have reported successful application of this method to the treatment of uremia following incompatible blood transfusion. Bloxsom and Powell[110] have successfully treated a case of uremia concomitant with acute glomerulonephritis, and Pearson[111] reports its trial in a case of carbon tetrachloride poisoning. Marsden[112] has reported its use in an interesting case of eclampsia. Odel and Ferris[113] give an excellent review of 27 cases collected from the literature and report 1 case of their own.

The clinical application of this form of treatment is becoming a widely accepted procedure, but it requires careful planning to avoid the pitfalls of water and electrolyte unbalance, of infection, and of poor timing. The dialyzing fluid must be prepared in great volume. The addition of sodium bicarbonate and antibiotics just before the fluid is used is clumsy and increases the possibility of contamination. The composition of the fluid must be carefully planned to contain all the ingredients of the plasma, but its composition may have to be changed to meet individual needs. Glucose is added to prevent the loss of blood sugar, and as an osmotic balance to avoid undue absorption of water. The best method of use of antibiotics is still unsettled, and peritonitis is a definite risk. Heparin is usually added to the fluid to slow the deposition of fibrin,

but the efficiency of dialysis falls off rapidly after three or four days.

Muirhead, Small et al.[114] report 3 cases in which they encountered one or another of these complications. In 1 case too much sodium chloride was absorbed, and the edema increased until distilled water was substituted and 70 gm. sodium chloride subsequently removed in this way with copious diuresis following. In another case, after a transfusion reaction, peritoneal irrigation was begun early in hopes of preventing the development of azotemia. This condition was not avoided, however, and the renal lesion progressed in spite of irrigation, and edema and acidosis were continuous worries. A third case was also complicated by severe acidosis and edema. Rob and Richardson[115] have likewise emphasized these points. Robertson and Rutherford[116] have encountered pulmonary edema in a patient dying on the eighth day.

To combat some of these complications, Reid, Penfold and Jones[117] have successfully used intermittent peritoneal irrigation. This may prevent the formation of a channel between entrance and exit tubes, which often takes place with continuous irrigation.

For control of peritonitis, most authors recommend the addition of penicillin, streptomycin or sulfonamides to the fluid, but Reid[117] has discarded penicillin as having an irritating effect on the peritoneum, which, by causing exudation, might interfere with free osmosis.

In summary, it may be said that peritoneal irrigation should be reserved for cases of acute renal insufficiency in which the process is likely to be reversible and only after more conservative measures have failed.

Intestinal Lavage

In an effort to find a safe, effective means of dialyzing water and crystalloids across a membranous surface of the body, numerous investigators have used various segments of the gastrointestinal tract.

Kolff[118] and Daugherty, Odel and Ferris[119] have concluded that the colon is unsuitable as a dialyzing membrane in the treatment of uremia, but an isolated loop of small intestine can be used with more success. Seligman, Frank and Fine,[106] after comparative studies in animals, concluded that the jejunum is probably the most suitable segment of the intestine for dialysis.

Most of these authors[106, 118–121] have perfused various segments of the gastrointestinal tract in treating patients with uremia. The results do not seem to be as encouraging as those with peritoneal lavage, but the procedure has not been so widely applied and many technical difficulties have to be overcome.

Renal Decapsulation

One of the numerous theories proposed to explain renal failure in toxic nephrosis is a decrease of the effective filtration pressure as a result of increased intrarenal pressure. Peters[70] recommends early decapsulation in severe cases and states that this procedure reduces the intrarenal pressure by 50 per cent. One point against this theory is that it does not explain the spontaneous diuresis on the tenth to the twelfth day when fluid retention is maximum. A more reasonable relation to the onset of the diuresis appears to be the fact that the tubular epithelium begins to regenerate soon after injury and is often adequately healed by the fourteenth day. Reports of a few cases successfully treated by this method have recently appeared in the literature including one by Reid, Penfold and Jones[122] in which peritoneal irrigation was combined with renal decapsulation.

Culpepper and Findley,[123] in an excellent review of the subject, discuss numerous cases of decapsulation and report an over-all mortality of about 50 per cent. They suggest that decapsulation of one kidney is as effective and less dangerous than a bilateral operation.

Spinal Anesthesia or Splanchnic Block

Trueta and his co-workers[90] have clearly demonstrated that reflex stimulation of the splanchnic nerves can divert the renal circulation from the cortical glomeruli. After section of the splanchnic nerves, this effect is reversed, and injury leads to a dilated cortical circulation. It is suggested that renal failure in the crush syndrome and allied conditions are of neurogenic origin and that they should be treated by spinal anesthesia or splanchnic block.

Several recent reports describe successful use of these methods in the treatment of acute renal shutdown. O'Sullivan and Spitzer[124] have successfully treated 2 cases of postabortion anuria with spinal anesthesia. Williams[125] reports a case of renal failure due to Weil's disease, in which diuresis continued after the effects of spinal anesthesia had worn off. This patient went on to recover. Robertson[126] has reported 3 cases of renal failure secondary to Weil's disease treated by this method, with 1 recovery and 2 deaths. In the fatal cases, the spinal anesthesia was carried out very late in the course of the disease.

Hingson and his co-workers[127] have had some interesting results with continuous caudal and spinal anesthesia; 35 patients suffering from anuria due to various causes, including eclampsia and acute vascular accidents, were treated. There were 8 deaths, 2 being among eclamptic patients, and in 2 it is possible that the splanchnic block contributed to the fatal outcome. It seems possible to keep up a continuous block for ten days, — that

is, to the crucial period, — after which the kidneys may resume normal function.

* * *

These observations bring out the important interdependence of the cardiovascular system, the autonomic nervous system and the kidney, and emphasize the need of consideration of the whole group of organs in renal malfunction or injury. Only rarely can an established renal injury be modified, but, guided by chemical and physiologic data, one can tide some patients over a critical period of renal insufficiency.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 34431

PRESENTATION OF CASE

First admission. A seventy-six-year-old woman was admitted to the hospital because of "pains in the stomach."

For many years the patient had attacks of momentary knife-like pain in the left upper quadrant of the abdomen, which never caused her much concern. About ten months before entry, however, she was confined to bed for three days with repeated attacks, each lasting about half an hour. These began with a sharp "ball of pain" in the left upper quadrant of the abdomen, which moved toward the epigastrium, "stabbing" as it went and accompanied by much gurgling. The pain then passed off. Also at that time she had a "large, black, slimy discharge" from the rectum. She had no nausea or vomiting. She was then well except for occasional pains until one month before admission, when she again had a three-day attack of the same type of pain. One week later she passed a tarry stool. She never tried food or alkali for relief of the pain, and she did not notice any loss of strength or energy during the present illness. She noted no difference in the character of the pain upon sitting or lying down.

Her appetite had been poor for eight years before admission, the change having been noted about the time of a "nervous breakdown," which followed her husband's death. She was put on a diet at that time and ate no vegetables, raw fruits, fried or fatty foods.

Physical examination revealed a woman in no acute distress but showing some evidence of weight loss. The blood pressure was 190 systolic, 80 diastolic. The rest of the examination was essentially negative.

Examination of the blood disclosed a white-cell count of 10,800, with 71 per cent neutrophils. The hemoglobin was 13.2 gm. per 100 cc. The red cells and platelets were fairly normal in appearance. The total protein was 7.1 gm., and the nonprotein nitrogen 26 mg. per 100 cc. The urine specific gravity was 1.016, and the sediment contained 3 white cells per high-power field. A stool was guaiac negative.

A barium enema revealed numerous diverticula throughout the entire length of the colon but more marked in the descending and sigmoid portions. There was a redundancy of the hepatic flexure of the colon, and the cecum lay high and was directed laterally. About 5 cm. from the cecal tip there was a constant constriction of the lumen over a length of about 2 cm. (Fig. 1). The mucosa within the lumen did not appear to be destroyed. The terminal ileum was not seen. A Graham test and an intravenous pyelogram were negative. A gastrointestinal series showed a normal esophagus with the patient in the erect position. However, with the patient in a prone position a large, readily reducible hiatus hernia was demonstrated, the cardia being situated above the diaphragm. The diaphragmatic hiatus was of good size but constricted the fundus slightly. No lesion was demonstrated within the herniated portion of the stomach, and the remainder of the stomach and duodenum was not remarkable. The small bowel was normal; the ileocecal region was not well shown.

After a stay of two and a half weeks in the hospital the patient was discharged to return in two months for another barium enema.

Second admission (approximately two months later). In the interval the patient had felt improved although she did not find the prescribed diet palatable. She had two attacks of crampy, sharp pain in the left upper quadrant of the abdomen, each lasting about three days and unassociated with nausea, vomiting, diarrhea or constipation. She had no tarry or bloody stools.

Physical examination showed, in addition to the findings of the first admission, slight tenderness in the left upper quadrant of the abdomen. The cecum was questionably palpable. The abdomen was protuberant and tympanitic, with hyperactive peristalsis of moderately high-pitched character.

Examination of the blood disclosed a white-cell count of 9300, with 74 per cent neutrophils. The hemoglobin was 9.7 gm. The stool was guaiac negative.

A plain film of the abdomen showed a suggestion of fullness overlying the sacrum extending somewhat to the right and about which ran a loop of small bowel. A barium enema revealed no abnormalities except diverticula until a redundant hepatic flexure was passed and the distal portion of the ascending colon entered. There the barium encountered an obstruction with narrowing of the lumen of the bowel but with many mucosal folds still apparent in that region. A gastrointestinal series confirmed the previous finding of a hiatus hernia that filled and emptied well. The remainder of the stomach was normal, as was the small bowel, with the exception of one persistent loop in the right lower quadrant, which appeared to be held in relatively constant position by an oval mass in the right lower quadrant (Fig. 2). The proximal

portion of the large bowel demonstrated a constricting lesion in the ascending colon at the level of the apparent mass that fixed the small bowel.

On the twelfth hospital day an operation was performed.

Differential Diagnosis

Dr. Richard Schatzki: I have been given a large number of films and have selected some of them for demonstration. I am in the position of the radiologist who has to rely on films of the gastrointestinal tract that somebody else has taken and somebody else has seen the fluoroscopy and taken spot films. If that person did not see the actual lesion, I am out of luck because I will not have films of the lesion. If he has seen it and has taken inadequate films, I am still in trouble. I am probably in trouble anyhow.

In summarizing the history one can say that in ten or twelve months this woman had two attacks of severe left-upper-quadrant pain, bled twice and ended up by having a slight anemia.

As far as the question of bleeding is concerned, I have a spot film of the lower end of the esophagus that fails to show varices, and since I cannot see

Figure 1.

any in the film, I am not going to think any more about them. The most common source of bleeding in a patient with tarry stools is duodenal ulcer. There are a few spot films of the duodenum that do not show any abnormality. Although it is possible that on such films an ulcer might be missed, I am going to discard this diagnosis. Hiatus hernia is a source of bleeding. I am usually, however, not satisfied to accept a hiatus hernia as the source of bleeding because I am convinced that it is not a very common source of massive bleeding. So for the sake of this discussion I am going to say that I do not believe that this patient bled from a hiatus hernia.

The patient had numerous diverticula in the colon. Diverticulosis, particularly diverticulitis of the colon, is supposed to cause hemorrhage. Again, I am unhappy if I cannot find any other source of bleeding in a patient but diverticulosis or diverticulitis. The recent surgical literature talks about bleeding in diverticulitis as if it were very common. Personally, I am convinced that it is not common

Figure 2.

although it does occur. I do not believe that this patient bled from diverticulosis, particularly since she had tarry stools.

I would like to find something in this patient's left upper abdomen. In looking through the films I have not been able to see anything there that might cause the symptoms.

Some other things might be mentioned. She had extensive arteriosclerosis of the abdominal aorta and its branches. She had changes in the left femur that were probably due to Paget's disease.

So we come to the ileocecal region — the lesion described in the record is not an area that one can understand from the films that we have. The abnormal position of the ascending colon is seen. The tip of the cecum, if this is the tip, is not the lowest point of the right colon but lies posteriorly

behind the ascending colon. There are some spot films showing this constriction, which is very uncharacteristic, certainly in its shape. It does not simulate primary carcinoma of the colon. In this spot film it is conceivable that a smaller cancer is behind in the tip of the cecum, but I cannot see that in these films. The lateral view gives a better position of the cecum and ascending colon with the narrowed zone. There are many films of the small bowel. At least ten films of the small bowel were given to me. In none of them can I see the actual terminal few inches of the ileum and the actual ileocecal valve. When one looks at the loops of small bowel in the films taken at the time of the first admission and compares the pattern of the arrangement of loops of small bowel, one has the impression that the pattern does change to some degree —not quite so much, however, as it does in the average patient with a normal peritoneal cavity. This loop, for instance, is present in both these films in a similar position. In other words, I have from these films the same impression given in the reports: that these loops were not freely movable but were for some reason fixed. The soft-tissue mass described in the report is not too obvious. One can see here the loop of small bowel described as running around the soft-tissue mass. There is one piece of bowel seen on only one film that I cannot explain. It looks as if it were locally dilated. If it is small bowel, it looks as if it were probably terminal ileum, and I think its proximal end was not demonstrated; this may be due to disease. Here, on another film, this might be the same loop. It is not quite so dilated, and it again ends up before it reaches the cecum. At the last examination the cecum had changed little. One still sees the constriction here, which I think is probably in the region of the ileocecal valve. On some of these films a peculiar swelling just distal to the constricted area is apparent.

To summarize the x-ray findings, after discarding the ones I decided were of no significance, I find a lesion in the region of the ileocecal valve, but I am not certain whether it started on the cecal side or on the side of the ileum. I am not certain how it looks because I am not certain I actually see the lesion. If it is in the cecum, I do see it, and it would be a very unusual type of tumor. If it starts in the ileum, I do not believe it is ileitis from the evidence we have here, but it is probably a tumor. There is, however, an outside chance that it is tuberculosis, which also might explain the changes in the peritoneal cavity. I would say first that this was a tumor of the ileocecal valve and secondly, as an outside possibility, tuberculosis. As a matter of fact, I never remember having seen a patient with tuberculosis with massive hemorrhage, but I suppose it can happen.

I looked over all the films of the stomach, and something has been worrying me for a while. The stomach appears on these films not quite so flexible as the average stomach does when several films are taken. It does not quite fit the shape of a normal stomach. It looks as if it might be infiltrated. From the evidence at hand I do not see any way of making a diagnosis of scirrhous carcinoma of the stomach. Again, I am forced from the evidence at hand to forget about the stomach. I shall not try to go any farther histologically because I am a little uneasy about the actual shape of the lesion.

DR. TRACY B. MALLORY: Would you be willing to hazard a guess whether the tumor in the region of the ileocecal valve is benign or malignant?

DR. SCHATZKI: If I guess, I do so against my roentgenologic conscience because I am making a pure guess without actually seeing the lesion correctly. Statistically I should say that it is cancer. There are, however, a few things that are a little peculiar and make me think it very well may not be a straightforward cancer. One reason for my statement is the apparent good clinical condition of the patient with a history of twelve months' duration; the second reason is connected with the fact that attacks of partial obstruction lasted over such a long period. Obstruction due to cancer of the ileocecal valve usually persists once it is established. The history in this case might, therefore, be interpreted as consistent with benign tumor. If I wanted to guess further, a common benign tumor in that area would be carcinoid. Yet I do not know that a carcinoid could produce so much bleeding, but I think it could. Am I right about that?

DR. MALLORY: Carcinoids almost never ulcerate the mucosa.

DR. SCHATZKI: In other words, it will not bleed. The most common benign tumor in the small bowel or in the colon to bleed is an intramural, extramucosal tumor. I do not have any right to make that diagnosis unless I put more stress on the soft-tissue mass than I believe I have a right to from the evidence at hand.

DR. ALLEN G. BRAILEY: How do you explain the left-upper-quadrant pain, Dr. Schatzki?

DR. SCHATZKI: The only possible explanation is that when the patient had pain she had partial obstruction with the hyperactive area of bowel in the left upper quadrant rather than the right. Usually, a patient with ileocecal obstruction has pain on the right side.

CLINICAL DIAGNOSES

Diverticulitis and diverticulosis of descending colon, with partial large-bowel obstruction.
Hiatus hernia.
Neoplasm of ascending colon?

DR. SCHATZKI'S DIAGNOSIS

Tumor of ileocecal valve, possibly carcinoid.

Anatomical Diagnosis

Carcinoid of ileum.

Pathological Discussion

Dr. Claude E. Welch: I must congratulate Dr. Schatzki on his diagnosis. This was a very difficult problem clinically. When the patient first came to the hospital we thought that her symptoms were due to diaphragmatic hernia, accounting for the left-upper-quadrant pain and, apparently, for the gastrointestinal bleeding. She had, in addition, this defect in the cecum. Our attention was focused high on the ascending colon over this area seen in the first film, which I thought could be due to adhesions around an old diverticulitis. The question arose whether to operate on the strength of this x-ray finding or whether, at the age of seventy-six, she might be relieved by diet. We therefore sent her home for a two-month period to return for further evaluation. She modified her diet to the point where it included only water, which probably accounted for the secondary anemia, since the stools remained guaiac negative. Since at the second admission the same defect in the cecum was manifested and she did have an episode of distention, it seemed wise to explore her. At operation there were numerous adhesions in the right lower quadrant, a diaphragmatic hernia and diverticulitis. The remainder of the abdomen was normal except for the region of the ileocecal valve, where, in the midst of the adhesions, was a rather indefinite palpable mass. One definitely dilated loop of the terminal ileum was tied up in the adhesions. The rest of the small bowel was entirely normal. I did a right colectomy on her in one stage. Dr. Mallory will give us the final report. It is only fair to state that we do not know yet whether or not the pains will be relieved by the operation. She is relieved of the disease in the right lower quadrant. The pain may have been due to the diaphragmatic hernia.

Dr. Schatzki: How often does pain in the left upper quadrant occur with a diaphragmatic hernia?

Dr. Welch: The pains were repeated, postprandial attacks. It is not too uncommon to have pain of that type with diaphragmatic hernia.

Dr. Mallory: The lesion that Dr. Welch resected was in the terminal ileum, immediately adjacent to the ileocecal valve. It was a tumor lying in the submucosal wall of the ileum. It extended through the wall into the mesenteric fat, and it had produced numerous adhesions. There was no actual tumor of the cecum. The tumor histologically was characteristic of carcinoid. There were numerous enlarged mesenteric lymph nodes, but none of them showed metastases. These carcinoids of the ileum do actually metastasize but usually not to any great distance. Not infrequently they metastasize to the immediately adjacent mesenteric lymph nodes.

Dr. Schatzki: What caused the bleeding?

Dr. Mallory: There was no evidence of ulceration of the mucous membrane overlying the tumor, and I am not at all sure that we have an explanation for the bleeding.

Dr. Schatzki: How large was the lesion?

Dr. Mallory: The actual tumor was 1.5 cm. in diameter — not very large.

CASE 34432

Presentation of Case

First admission. A thirteen-year-old schoolboy entered the hospital complaining of frequent bowel movements.

For about one year prior to admission he had experienced rather constant diarrhea, with up to seven evacuations daily, unassociated with pain or bleeding.

Physical examination was essentially negative.

The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 3,630,000, with 40 per cent hemoglobin, and a white-cell count of 10,300, with 50 per cent neutrophils, 46 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The specific gravity of the urine varied from 1.008 to 1.028. The urine was negative for albumin, casts and cellular sediment. Two stool cultures were negative for pathogens, and an examination for amebas was negative. An x-ray film of the heart and lungs was noncontributory, and a barium enema showed extinction of the haustral markings with narrowing of the lumen and shortening of the bowel. On proctoscopic examination scattered pin-point, shallow ulcerations with fine hemorrhages were seen.

The serum nonprotein nitrogen was 19 mg., and the total protein 6.3 gm. per 100 cc., and the chloride 104 milliequiv. per liter. A blood Hinton test was negative.

During the patient's hospital stay of two months he was given sulfasuxidine, tincture of belladonna and two transfusions. He improved slowly and gained weight, and his bowel movements decreased to one or two a day.

Second admission (two and a half years later). During the interval the patient visited the Out-Patient Department regularly and gained about 20 pounds, although his diet was apparently not adequate in protein. One week before entry, following a cold, he developed slight abdominal swelling, anorexia and vomiting. He also noted swelling of the legs and scrotum. The urine was darker than previously.

On physical examination the abdomen was distended, with a well marked fluid wave. The liver edge was palpable two or three fingerbreadths below

the right costal margin. There was slight edema of the scrotum and ankles.

Examination of the blood revealed a red-cell count of 3,440,000, with 11.4 gm. of hemoglobin, and a white-cell count of 8350, with a normal differential. The specific gravity of the urine was 1.030, with a ++++ test for bile, and a +++ test for albumin; the sediment contained innumerable red and white cells and hyaline and granular casts. The alkaline phosphatase was 19.8 units, the thymol turbidity 7.8 units and the thymol flocculation ++++. The serum total protein was 6.76 gm. per 100 cc., with 3.02 gm. of albumin and 3.74 gm. of globulin. A cephalin flocculation test was +++ at twenty-four and forty-eight hours, and there was 36 per cent retention of bromsulfalein.

The patient remained in the hospital for about nine weeks, receiving four transfusions and therapy directed toward amelioration of kidney and liver disease. On discharge, however, the bromsulfalein retention was 52 per cent, and the serum albumin 2.98 gm. per 100 cc. The urine showed a + test for albumin, with 10 to 15 red cells per high-power field and moderate hyaline and granular casts in the sediment.

Final admission (one and a half years later). During the interval the patient re-entered the hospital three times because of return of edema and ascites. His bowel movements had been controlled fairly well, averaging two or three a day. On these admissions he was given concentrated human albumin with satisfactory release of fluid. He also developed some swelling of the breasts during this period. He persistently showed some albuminuria, an increased cephalin and thymol flocculation and an altered albumin-globulin ratio, except following administration of concentrated albumin. About ten days prior to his final readmission he began to have anal pain and later complained of a "gassy" feeling in the stomach, followed by severe and persistent vomiting for four days.

On physical examination he retched occasionally during the interview but did not vomit. The abdomen was distended and flat to percussion throughout. There was pitting edema of the legs.

The blood pressure was 100 systolic, 50 diastolic.

Examination of the blood showed 5 gm. of hemoglobin and a white-cell count of 60,000, with 97 per cent neutrophils and 3 per cent myelocytes. Severe toxic granulation of the polymorphonuclear leukocytes was present. There was marked hypochromia and polychromatophilia, with 5 to 10 nucleated red cells per 100 nucleated cells. The urine specific gravity was 1.010, a ± test for bile was present and there were 2 or 3 hyaline casts per high-power field. The serum nonprotein nitrogen was 103 mg. per 100 cc., the carbon dioxide 22 milliequiv. and the chloride 88 milliequiv. per liter. The total protein was 3.68 gm. per 100 cc., with 1.08 gm. of albumin. The prothrombin time was 39 seconds (normal, 16 seconds), and the cephalin flocculation test was +++. A van den Bergh reaction was 3.2 mg. per 100 cc. direct and 4.3 mg. indirect.

Following admission three blood transfusions were administered. An abdominal paracentesis yielded 80 cc. of clear, straw-colored fluid, showing 30 cells per cubic millimeter and no organisms on direct smear. The temperature, which was normal on admission, remained about the same. On the fourth day the patient became rather drowsy, and on the following day he became disoriented and died.

Differential Diagnosis

Dr. Charles L. Short: At the time of this patient's first admission, at the age of thirteen, the picture certainly was that of chronic ulcerative colitis from the clinical and proctoscopic and x-ray findings. May we see the films?

Dr. James J. McCort: X-ray examination of the colon revealed a rigid and shortened large bowel. The haustral markings are scant. In the rectosigmoid region one can see small ulcerations in the wall of the colon. Even after evacuation a normal mucosal pattern is not seen. The changes are consistent with a chronic ulcerative colitis. Examination of the chest made, I believe, before the final admission shows marked elevation of the diaphragm due to the increased intraperitoneal fluid and also a small amount of fluid in the costophrenic sinus. The lungs, so far as we can see, are clear.

Dr. Short: Is there an examination of the small intestine?

Dr. McCort: No examination was made. There was no filling of the small bowel at the time the barium enema was performed.

Dr. Short: In this patient's first admission there was no real evidence of the renal or hepatic disease that later made its appearance. Two and a half years later, just before the second admission at the age of fifteen, ascites and edema rather suddenly developed. There is nothing in the record regarding clinical jaundice or whether or not he had increased bilirubin in the blood; but at least he had bile in the urine. Liver-function tests were those indicating severe parenchymal liver disease. In addition, and I believe not accounted for on the basis of liver disease, he had marked albuminuria with casts and large numbers of red and white cells in the urinary sediment. These findings certainly point toward renal disease and fit most closely with glomerulonephritis. The colitis was apparently mild after the patient's discharge, but the evidence of liver and renal disease persisted. At the time of the last admission, at the age of seventeen, the urine showed a low specific gravity on one examination at least and absence of cellular elements in the sediment, and for the first time he developed nitrogen retention. It is interesting that with the

high white-cell count there was no obvious evidence of sepsis and the abdominal tap did not disclose peritonitis, at least in the region where the tap was made.

I think that it is clear that this patient had disease involving at least three organs of the body. It is difficult, for me at least, to think of one diagnosis to explain all three conditions. I shall probably have to be content with several diagnoses and assume that there may be more than a coincidental relation among them. As you know, there are many extra-intestinal complications of so-called idiopathic chronic ulcerative colitis. Among the rarer ones are nephritis and parenchymal liver disease. Although the odds are perhaps against the coexistence of both these complications in the same patient, there is no reason why this situation should not take place. In one series of patients with ulcerative colitis, nephritis was reported in 13 per cent,[1] and in another, 1 per cent.[2] We do not know the exact nature of the renal lesion. In another series of patients with ulcerative colitis liver disease was recorded in 3 per cent,[3] thus making it a rare complication. There have been a few biopsies and post-mortem examinations of patients with this complication, but there has been no uniformity, as far as I can tell, in the findings. The condition is described as portal cirrhosis, chronic hepatitis and even hypertrophic biliary cirrhosis. In some cases the colitis has been mild, and the liver disease the most disabling condition.

Another possibility is that the patient had amyloidosis, secondary to long-standing chronic ulcerative colitis. This is also a rare complication of ulcerative colitis, but we have had at least 1 case in this hospital. The renal lesion could be explained on this basis. A feature against amyloidosis, but not necessarily ruling it out, is the degree of hematuria at the time of this patient's second admission. Although amyloidosis, if present, commonly involves the liver, the function of this organ is usually well preserved so that jaundice, ascites and laboratory evidence of depressed liver function are not usually recorded. There are, however, occasional exceptions, chiefly in the primary systemic type of amyloid disease. This brings me to the possibility that this patient had a primary type of amyloidosis, with amyloid infiltration of the intestinal wall simulating chronic ulcerative colitis. Diarrhea and intestinal bleeding have been described in systemic amyloidosis but never, so far as I know, a picture so closely resembling idiopathic ulcerative colitis as is seen in this patient. The terminal blood findings in this patient are of some interest. The presence of immature red cells suggests a myelophthisic anemia, with the remaining marrow overactive. Could this have been a response to amyloid infiltration in the marrow? The high white-cell count suggests sepsis, but the location is not clear. Or there could have been a venous thrombosis, perhaps in the portal system. Although the single diagnosis of amyloidosis is appealing in explaining to us most of the picture, I have decided to reject it as far as the liver is concerned. The reason for this is that amyloidosis rarely causes liver failure, but when it does it is more on a mechanical basis, with squeezing out of the liver cells and obstruction of the bile canaliculi. Early evidence of severe liver damage would be against the diagnosis of amyloidosis of the liver in this patient.

We are left then with the diagnosis of ulcerative colitis, idiopathic type, and liver disease. In view of the persistent evidence of liver-cell damage, I think that I will call it toxic cirrhosis rather than cirrhosis of the portal or biliary types. In fact, the terminal episode may have represented severe, widespread liver necrosis. In regard to the renal lesion, although I think that it could well have been due to amyloidosis, in view of the findings in the urinary sediment at the time of the second admission, I shall put glomerulonephritis ahead of this diagnosis. I shall not try to discuss the possible relation of all three conditions. If my diagnosis is correct, I think that a relation is possible but on a rather hypothetical basis. Finally, it would be very helpful to have had some Congo-red tests on this patient.

DR. TRACY B. MALLORY: Obviously this is an extremely difficult case. Does anyone wish to make an alternative diagnosis?

DR. DANIEL S. ELLIS: I followed this patient, and I might say that, although he had three apparently serious diseases, at no time did he ever have any conception of how sick he was. It is of interest that he was accepted in the National Guard and did three weeks' duty at Camp Edwards within two months of the final and fatal admission. The only way they found out he was sick was that he caught a cold and went on sick call and urinalysis revealed albumin, so they sent him home. He was indignant with the armed forces and the country in general because a strapping fellow like himself should be rejected. The last year of his life was possible because of the availability of human serum albumin. No other diuretics were effective. This boy had no symptoms during this period other than anasarca, which would gradually increase until it became incapacitating. Then he would come to the hospital for a course of 300 gm. of albumin and be discharged at the end of a week with a sufficient sense of well-being to go cheerfully back to school for another period.

In answer to Dr. Short's question: at the time the liver disease was manifested he was icteric. Those who were following him thought that he had chronic ulcerative colitis, that he developed acute hepatitis, and went on to a toxic cirrhosis, and that he probably died of acute nephritis, progressing to subacute or chronic stage.

DR. JACOB LERMAN: I saw him on the ward during the second admission and I tried very hard to make one diagnosis fit all the findings, but it was difficult. Of course, we thought that amyloid disease would be the best bet. I do not know why it was omitted from the record but there were three or four Congo-red determinations, and all were within normal range. So we thought that he had three separate diseases: nephritis, ulcerative colitis and toxic cirrhosis.

DR. EARLE M. CHAPMAN: I likewise saw this patient on the service, and I had a different idea from the previous visiting man who saw the patient. He had dissociated the liver disease and thought it was not related to the ulcerative colitis. I thought of tying them together. I raise the question whether therapy had anything to do with the renal lesion, which Dr. Mallory will describe. Was it related to the intensive intravenous therapy with albumin and other things that he received? I would be interested to hear Dr. Mallory's comments on the possible etiology of the renal lesion.

DR. ELLIS: The patient developed the renal damage before he received the albumin.

DR. LERMAN: I agree. The albumin was given on the second admission, and the renal damage had already been established. He did have sulfadiazine, however. Do you think that may have had any etiologic relation?

DR. MALLORY: Were any transfusions given before the second admission? Plasma or whole blood?

DR. SHORT: The record states that he had one.

DR. MALLORY: One and a half years is too long an interval for serum hepatitis.

DR. LERMAN: There was a two-and-a-half-year interval between the first and the second entry.

DR. ELLIS: He had none during that time.

CLINICAL DIAGNOSES

Cirrhosis of liver, toxic.
Cholemia.

DR. SHORT'S DIAGNOSES

Chronic ulcerative colitis.
Toxic cirrhosis of liver.
Glomerulonephritis.

ANATOMICAL DIAGNOSES

Chronic ulcerative colitis, severe.
Cirrhosis of liver, toxic type.
Acute glomerulonephritis.
Hemorrhage from esophageal varices.
Anasarca.
Gynecomastia.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination confirmed the three separate lesions: chronic ulcerative colitis, a severe degree of cirrhosis of the liver, of the grossly nodular, postatrophic type that here we call toxic cirrhosis, and acute glomerulonephritis. The immediate cause of death was hemorrhage from ruptured esophageal varices. From there on I think one must pass into the realm of speculation. A large proportion of patients with severe ulcerative colitis develop fatty livers before death, and on two occasions I can remember having seen the lesion progress into a mild degree of fatty cirrhosis of the finely granular type, which we usually associate with a history of chronic alcoholism. This probably was not that type of cirrhosis. I do not know any direct way of connecting the liver and the renal disease. There is enough element of sepsis associated with ulcerative colitis to make it not unreasonable that an occasional case should develop glomerulonephritis, but I think we have to consider that a separate complication and I do not see how we can tie the liver and the kidney lesions together with one mechanism.

DR. ALFRED KRANES: Is there anything to account for the extreme leukocytosis?

DR. MALLORY: The bone marrow showed only very marked diffuse hyperplasia. There were a considerable number of small pulmonary emboli, but since there was very little infarction embolism hardly seems a good explanation for leukocytosis. The renal lesion did not progress very far. It was an intracapillary type of glomerulitis with no crescent formation and no secondary changes in the tubules; it did not appear particularly active.

DR. SHORT: Was the liver process very active at the time of autopsy?

DR. MALLORY: No; the picture was variable in the different lobules, but on the whole it looked like a healed scar and not an actively progressive process.

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BOSTON UNIVERSITY SCHOOL OF MEDICINE

1848–1948

Boston University School of Medicine, in celebrating its hundredth anniversary this month, recalls with pride that its original foundation was based on the idea of higher education for women. On November 1, 1848, the Boston Female Medical College, the first of its kind in the United States and probably in the world, began its instruction in medical subjects; three years later it changed its name to New England Female Medical College. The entering wedge had been driven, and the right of women to enter the professions acknowledged.

The Massachusetts Medical Society, a bulwark of conservatism, was in opposition. Nevertheless, many of the professors of the new school were members of the Society and graduates of Harvard. The first woman professor, Dr. Marie E. Zabrzewska, appointed in 1859, became later one of the founders of the New England Hospital for Women and Children.

At first an institution that merely gave instruction in medical subjects, the new college in 1852 inaugurated its complete course leading to the degree of Doctor of Medicine. The first class, of four women, graduated in 1854. Many women attended sessions without graduating, some leaving to enter practice without a degree, and others to become midwives, nurses or teachers of physiology.

In 1870 the School erected a permanent building on East Concord Street that is still in use as part of Boston University School of Medicine. In 1873 the most important step was taken that the School had yet made: the joining of forces with the infant Boston University and the Massachusetts Homeopathic Medical Society, which had been organized in revolt against the drastic empiricism of "regular" medicine of the day. The School, its original function discharged, became coeducational and homeopathic. During this year, also, an amphitheater was provided that was to serve the classes for the next seventy-five years.

An optional four-year course in addition to the required three years was instituted in 1878, and in 1890 this was made obligatory — a pioneer requirement in America. In 1918, homeopathy having achieved its logical purpose of breaking down a dogma from the past, Boston University School of Medicine became nonsectarian.

The clinical teaching facilities of the School have been impressively increased. The John C. Haynes Memorial for Contagious Diseases was opened in 1909, the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine in 1911, and the Jennie M. Robinson Maternity Department in 1916. Extensive teaching affiliations have been established with the Boston City Hospital, various state hospitals, the Judge Baker Guidance Center, the James Jackson Putnam Children's Center and St. Margaret's Hospital.

May the future be as rewarding as its diversified past has been to this eminent school of medicine!

THE EFFICIENCY OF MEDICAL SERVICE

FAMILY doctors have ample opportunity these days to see themselves as others see them. From such an emotional outlook as that of Ian MacLaren it was a heart-warming view, and many a patient continues to share it with those who knew the horse-and-buggy doctors at their best. In many of the mirrors held up to the physician of today, however, there is an emotional screen that removes all trace of sentiment and feeling.

The industrial or business point of view is one where efficiency sits enthroned, and where lack of efficiency is viewed with impatience. Doctors, in their daily lives, are inclined to place a higher value on the end result than they do upon the efficiency with which it is achieved. In matters seriously involving life and limb this attitude is understood and is even encouraged by thoughtless people when they tell the doctor that he is to "spare no expense" in this and that, believing that the more the service costs the better it must be. People believe this because they may have no better method of appraisal. Modern industry wants the best results too; it not only is beginning to demand them but also is aware of the fact that the efficiency with which they are achieved is a measure of their value, and to some extent of their quality as well. Although industry still employs largely the private doctor, and upon his own terms too, his methods as well as his results are being scrutinized by businessmen, by labor leaders, by engineers and by other physicians all of whom are geared to modern industry's heartless demand for efficiency as well as for good results.

How may the quality of medical service be appraised? The answer depends upon the critical capacity of the appraiser. There are probably more ways of judging medical service than there are of judging horseflesh; some are good and some are not. What is a good method for one situation may not be for another. When much is known and appreciated about the self-limitation of disease there may be created an entirely different standard of judgment. On the whole, medical service may be said to be judged by informed public opinion, and public opinion is becoming more informed every year.

Doctors practicing in a certain locality may see themselves as the industrial physician sees them by reading Shipman's article in this issue of the *Journal*. They should remember that the author is naturally trying to emphasize the points at which friction occurs. These points are not peculiar to that industry or that region; in fact it is pointed out that similar occurrences have been noted in California. These little conflicts of opinion, of judgment and of action are rooted deep in human nature, in the competitive spirit of man and in the circumstances of the environment in which we all must live, and strive to live together.

Not only industrialists but also welfare boards, insurance carriers and compensation authorities are vividly aware of medical efficiency, or its lack, in the care of the patients in whom they are interested. When a welfare official finds that 90 per cent of the money paid in a small community goes to a single doctor (on a fee-for-service basis) and that his patients do not seem to have more serious ailments or different end results than those of the other doctors, that official is rightly suspicious of that doctor. Such doctors are scattered here and there, generally believing themselves smart in their padding activities. They are notoriously well known among people whose business it is to handle financial adjustments that involve medical services. Inefficient is a very polite adjective to describe this type of medical practice.

HORNS OF THE DILEMMA

WITH pardonable pride, a doctor may fancy his lifework the most important in the world — especially if he is very young. When combined, as that belief usually is, with idealism and optimism and energy, it is not only pardonable but also admirable. If the youth had less regard for his profession, and less energy and idealism in its pursuit, he would not be worth his salt. Later as he measures himself against the world he finds that other activities, especially the more effective means of getting and spending, are highly esteemed, and discovers that his profession is not the most efficient

in these pursuits. Still he is received everywhere by all conditions of men, and finds that most people are more than friendly. Men render him a rather special devotion because he is thought to be less material, less grasping, more ready than others to sacrifice his own comfort and welfare to that of those whom he serves. Presently he realizes a little sadly that this high opinion bears very little relation to his cash income.

The busy average doctor at the moment feels acutely in his pocketbook the rigors of the current inflation. He is therefore peculiarly interested in, or perhaps susceptible to, economic propaganda. There is plenty of it within the profession, but he has seemingly only two choices. He may listen to the National Physicians Committee or to the Committee of Physicians for the Improvement of Medical Care or, more lately, to the Physicians Forum, and, depending on his bias at the moment, may fancy that he hears the voice of red medicine or of medical fellow travelers or at least of the intellectual pinks. To confuse him further and cut down his ego, he finds that his future is being planned by Congress, sociologists and popular writers. Unpleasant comments come from almost every quarter. Some of his colleagues managing a blood bank are accused of profiting in their traffic and of being no better than vampires. He may be shocked by the statement of a wealthy elder statesman and doctor's son: "I do not fear Government taking its legitimate part in medicine, any more than I fear it in education or housing . . . I urge the doctors to get in and pitch — not stand by on the sidelines."

Precisely what is the doctor's economic and social status? Economically he belongs to the middle class, which is being threatened from both above and below. The division of the more vocal colleagues into far-right and far-left groups is just what is happening in general society. Some name calling is already being indulged in. Unless physicians are circumspect, they may have to face witch hunts and loyalty checks or even public trials for subversive activities. According to Toynbee,* the position of the middle class is in question now in all western countries.

*Toynbee, A. J. *Civilization on Trial.* Chapter 2, "Present Point in History." New York: Oxford University Press, 1948.

The middle class, really a tiny minority, has created the modern world with its technologic advances, its knowledge and its tremendous means of production. The still underprivileged majority is pressing the middle class for a fair share of the good things of life, including the "care services," of interest to all — namely, housing, social security and health. The world is caught in a conflict of ideas, and seemingly is being forced to choose between the extremes of unrestricted private enterprise, with inequalities of distribution, and unmitigated socialism, which alleges that it will divide everything equally.

Economically the physician is of the middle class, but socially he is without class. His science and his art are acquired, developed and applied without regard to nation, race, creed or personal reward. In his professional life the doctor traditionally is apart from the divisions among men. If class and war have always caused the breakdown of societies, and if there is full realization that these must be eliminated now to enable the civilization to survive, may not the medical profession play a role in finding the "middle way" between apparently irreconcilable extremes?

NEW ENGLAND POSTGRADUATE ASSEMBLY

The seventh annual postgraduate assembly of the New England state medical societies will be held at the Copley Plaza Hotel on November 3, 4 and 5. An interesting program with speakers of distinction in their special fields has been arranged and has already appeared in the *Journal* on September 30 and October 14. Particularly to be emphasized are the clinics that will be held at major Boston hospitals on the morning of November 5. The committee in charge, composed of representatives of the six New England societies, under the able chairmanship of Dr. Leroy E. Parkins, is again to be congratulated on the list of subjects and speakers that it has selected.

The New England Postgraduate Assembly, after seven years of operation in a country where events frequently succeed one another with startling rapidity, may be considered as a tradition. To be a

New England tradition is in itself a mark of distinction.

Each year the Postgraduate Assembly has surpassed its previous record in attendance and — a very tangible sign of success — its attractiveness to technical exhibitors. It should be to the advantage of the New England Council of State Medical Societies some day to take over the Assembly as its own project. Present indications suggest that the Assembly might even be able to furnish the Council with those fiscal assets so necessary to existence.

BLUE CROSS-BLUE SHIELD

MEDICAL SECRETARY MEETINGS

As part of the Blue Shield professional relations program a series of group meetings with medical secretaries is being conducted throughout the Commonwealth.

These group discussions are designed to provide medical secretaries with current and detailed information concerning Blue Shield benefits, claim report forms, Blue Shield income limitations, rules and regulations and other pertinent information that will help to minimize or eliminate errors, thereby providing better service to participating physicians and Blue Shield patients.

These informal discussions of mutual problems have proved to be very worth while. Meetings have been scheduled for approximately forty towns and cities during the next eight months.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REIMBURSEMENT OF PHYSICIANS UNDER EMIC PROGRAM

The Massachusetts Department of Public Health has received notification from the Children's Bureau, Washington, D. C., that all federal reimbursements for emergency maternal and infant care services, as authorized under the EMIC program, will terminate as of June 30, 1949.

That Massachusetts physicians may be assured reimbursement for such services, The Massachusetts Department of Public Health requests that all outstanding bills for care authorized under the Massachusetts EMIC program be submitted to the Division of Maternal and Child Health, Massachusetts Department of Public Health, 73 Tremont Street, Boston, not later than May 1, 1949.

Provision for maternal care under this program has been authorized for the period September 3, 1943, to April 4, 1948; for infant care such services will terminate as of April 4, 1949.

VACCINE FOR ROCKY MOUNTAIN SPOTTED FEVER

The United States Public Health Service has announced that it is discontinuing the manufacture of vaccine for Rocky Mountain spotted fever. This vaccine is now available from commercial manufacturers so that physicians who wish to use it will have no difficulty in purchasing the product.

For many years the Rocky Mountain Laboratory was the only source from which vaccine for this disease could be obtained. The first variety of the vaccine was prepared from the bodies of infected ticks and played an important part in reducing the numbers of cases and deaths in the valleys of the Rocky Mountains, where the disease had been prevalent for many years.

The tick-tissue type of vaccine has now been superseded by the chick-embryo type. The commercial manufacturers will be supplying only the new variety. When the present supply of tick-tissue vaccine on hand is depleted, the old variety will no longer be available. The Rocky Mountain Laboratory will make the tick-tissue vaccine available as long as the present supply lasts.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The November schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Clinic	Date	Clinic Consultant
Salem	November 1	Paul W. Hugenberger
Haverhill	November 3	William T. Green
Lowell	November 5	Albert H. Brewster
Gardner	November 9	Carter R. Rowe
Springfield	November 16	Garry deN. Hough, Jr.
Pittsfield	November 17	Frank A. Slowick
Brockton	November 18	George W. Van Gorder
Hyannis	November 18	Paul L. Norton
Worcester	November 19	John W. O'Meara
Fall River	November 22	David S. Grice
Greenfield	November 22	Charles L. Sturdevant

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

APPOINTMENT

Dr. Lendon Snedeker, of Brookline, has been appointed assistant administrator of the Children's Medical Center of Boston.

BODY BLOW

Blue Cross in British Columbia, according to an Associated Medical Care Plans release, will be forced to liquidate on December 31, 1948. This will mark the first time that a well established voluntary plan has been forced out of existence in North America by the advent of compulsory health insurance.

British Columbia's Blue Cross has been unable to meet conditions imposed by the provincial Government's new hospital insurance act.

UNITED STATES PUBLIC HEALTH SERVICE

To foster training of medical students in the mental aspects of disease, federal grants for undergraduate courses are now being offered to medical schools by the United States Public Health Service. Formerly, grants to medical schools, authorized by the National Mental Health Act, were utilized primarily for graduate training in psychiatry.

Extension of grants to the undergraduate field was recommended by the National Advisory Mental Health Council as a means of providing future physicians with basic knowledge that will help them to recognize early symptoms of mental illness, to treat cases that do not require the services of a specialist and to apply psychiatric principles in the treatment of all types of illness.

Applications must be made to the Mental Hygiene Division of the Public Health Service by October 15, 1948. Grants will cover a three-year period beginning July 1, 1949, and will be paid in annual installments.

WATER-POLLUTION ACT

The federal Government has finally been given the power to control stream pollution under the Barkley–Taft Water Pollution Act, passed as one of the last acts of the eightieth Congress.

Under the Act, *Scientific American* reports, the Federal Works Administration is permitted to lend states and municipalities up to one third the cost of new sewage-treatment and pollution-abatement facilities. A Public Health Service research and training center on pollution control is to be located in Cincinnati, Ohio.

Eight states — Illinois, Indiana, Kentucky, New York, Ohio, Pennsylvania, Virginia and West Virginia — have meanwhile signed a regional agreement to clean up the beautiful Ohio, a stream with the reputation of being the most polluted river in the world.

CORRESPONDENCE

THE FAMILY PRACTITIONER

To the Editor: Please let me thank you for your editorial "Down East Doctor," which I enjoyed very much indeed. I also want to tell you that I find the *Journal* one of the most informative and valuable that comes to my desk among a large number of medical and general publications.

The problem that you raised concerning the preservation of the general practitioner (I think "family practitioner" is a better term) is one to which all of us should give out best attention and intelligent effort.

It appears to me that many hospital trustees, hospital administrators, certain specialists and the American College of Surgeons, unwittingly I trust, are doing much that may lead to elimination of the family physician. The problem is one not only for small communities but also for large cities. I know of hospitals in which the general practitioner is not permitted to apply splints and bandages to uncomplicated injuries or assist in short operations or open superficial abscesses, not because he is incompetent to do these things, not because he is dishonest or unethical, not because he is not a gentleman, but solely because he is not a specialist.

It seems to me that this is one of our most pressing problems today. It is only, I think, through preservation of the family practitioner, that we can prevent state medicine, and I think you will agree with me that state medicine of itself will lead to a totalitarian government, which unquestionably would soon become a slave government. That, of course, is the lesson that history teaches so clearly, and we cannot expect anything else if we follow the same dismal path.

Again let me thank you for the excellent *Journal*.

MALCOM THOMPSON, M.D.

Louisville, Kentucky.

BOOK REVIEWS

Biochemistry of Cancer. By Jesse P. Greenstein. 8°, cloth, 389 pp., with 39 illustrations and 104 tables. New York: Academic Press, Incorporated, 1947. $7.80.

This book is much more comprehensive and varied than the subject indicates. Oncology is the author's term for cancer research. The "oncologic sciences" are clinical medicine, surgery, pathology, radiation, physics, genetics, immunology, endocrinology and biochemistry — in short, the entire field of medicine. Some of the definitions used are hardly those in common use by cancer practitioners. "The term carcinoma may be applied to tumors which arise from epithelial tissue" and "the term sarcoma may be applied to tumors arising from connective and muscle tissues." The author does not distinguish between benign and malignant tumors in making these definitions although in another section he enlarges on the close margin between malignancy and benignancy. Again, ". . . and the neoplasms which ensue are known as cancers or tumors." The writer raises an interesting hypothesis regarding the capacity of tumors for autonomous growth — that a benign growth is largely dependent upon the organism and hence not truly autonomous, whereas a malignant growth is largely autonomous and independent of the organism. He suggests that a cancer of the prostate that responds to hormone therapy is relatively nonautonomous and hence benign; later, it becomes refractory to treatment and is autonomous and thus malignant.

In the chapter on the general phenomena and taxonomy of cancer Greenstein deals with the experimental induction of tumors and mentions a few of the known carcinogenic agents such as tar, polycyclic hydrocarbons, azo dyes, zinc salts, radium salts, x-rays and cysticercus. He also refers to cancerous transformation of animal tissues in vitro, the growth and the vascular reactions of tumors, plant tumors, the melanomas of fish and tissue-immunity reactions.

One chapter considers the extrinsic chemical factors, — the chemicals that are known to induce cancer. Among these are 1, 2, 5, 6-dibenzanthracene; and 3, 4-benzpyrene. The technic used in studying and synthesizing carcinogenic hydrocarbons is described. Much work has been done in animals to determine the types of tumors induced, the susceptibility of different strains of the hydrocarbons and the fate of the injected hydrocarbons. Many deaths have occurred from cancer of the scrotum in workers exposed to coal tar.

Intrinsic factors are defined as agents that possess a biogenic origin, including hormones and viruses. The chemistry of hormones and similar synthetic preparations and the use of these materials in experimental animals are discussed.

Chemotherapy has been of little value in the therapy of cancer. Coley's toxins when first prepared and administered by Coley seemed of some help in certain cancer patients, but later the results could not be obtained by Coley or others. Polysaccharide injections and the use of Fowler's solution and colchicine offered high hopes, but all such methods have failed.

The author is at his best in discussing the chemistry of tumors, since much of the work mentioned has been done by him or under his direction. Extensive analyses have been made of the chemical structure of normal tissues and of neoplasms, the oxygen consumption of normal and neoplastic tissues, the activity of phosphatases, the glycogen content and many other subjects. Two hundred and forty-seven references are given for the material presented in this chapter.

Psychopathology and Education of the Brain-Injured Child. By Alfred A. Strauss, and Laura E. Lehtinen. 8°, cloth, 206 pp., with 46 illustrations. New York: Grune and Stratton, 1947. $5.00.

This monograph is based on research work conducted by the authors and in part previously published in various periodicals. The text is divided into two parts: psychopathology and teaching. The first part is prefaced with a historical review of the subject, followed by chapters on anatomy and function of the brain, perception and perceptual disturbances, thinking disorders, behavior disorders, testing and diagnosis of brain injury in children. The second part, on education, considers the general principles of education, and the teaching of arithmetic, reading and writing. An appendix presents a study of a deaf child with a brain injury by Mary A. Bair, an excerpt from an unpublished essay. The text is documented with a number of case histories. References to the literature are printed as footnotes on the appropriate pages. The book is well published and should prove of interest to neurologists and psychiatrists.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Tuberculosis: A discussion of phthisiogenesis, immunology, pathologic physiology, diagnosis, and treatment. By Francis M. Pottenger, A.M., M.D., LL.D., medical director, the Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, California. 8°, cloth, 597 pp., with 105 illustrations. St. Louis: The C. V. Mosby Company, 1948. $12.00.

The Epithelia of Woman's Reproductive Organs: A correlative study of cyclic changes. By George N. Papanicolaou, M.D., Ph.D., professor of clinical anatomy, Cornell University Medical College, Herbert F. Traut, M.D., professor of obstetrics and gynecology, University of California Medical School, and Andrew A. Marchetti, M.D., associate professor of obstetrics and gynecology, Cornell University Medical College. 4°, cloth, 53 pp., with 22 plates. New York: The Commonwealth Fund, 1948. $10.00.

Atlas of Plastic Surgery. By Morton I. Berson, M.D. 4°, cloth, 304 pp., illustrated. New York: Grune and Stratton, 1948. $15.00.

Diabetus Mellitus in General Practice. By Arthur R. Colwell, M.D., associate professor of medicine and director of medical specialty training, Northwestern University Medical School, attending physician, Evanston Hospital, Evanston, Illinois, and consulting physician, Wesley Memorial Hospital, Chicago. 8°, cloth, 350 pp., with 24 illustrations. Chicago: The Year Book Publishers, Incorporated, 1947. $5.25.

Telepathy and Medical Psychology. By Jan Ehrenwald, M.D. With a foreword by Gardner Murphy. 8°, cloth, 212 pp. New York: W.W. Norton and Company, Incorporated, 1948. $3.00.

Brief Psychotherapy: A handbook for physicians on the clinical aspects of neuroses. By Bertrand S. Frohman, M.D. With the collaboration of Evelyn P. Frohman, and with a foreword by Walter C. Alvarez, M.D. 12°, cloth, 265 pp. Philadelphia: Lea and Febiger, 1948. $4.00.

Case Histories in Clinical and Abnormal Psychology. [Edited by Arthur Burton, associate professor of psychology, Willamette University, and Robert E. Harris, associate professor of medical psychology, University of California. 8°, cloth, 680 pp. New York and London: Harper and Brothers, 1947. $4.00.

Hormones and Behavior: A survey of interrelationships between endocrine secretions and patterns of overt response. By Frank A. Beach, professor of psychology, Yale University. With a foreword by Earl T. Engle. 8°, cloth, 368 pp. New York: Paul B. Hoeber, Incorporated, 1948. $6.50.

The Treatment of Rheumatism in General Practice. By W. S. C. Copeman, O.B.E., M.A., M.D. (Cantab.), F.R.C.P. (London), physician in charge, Department of Chronic Rheumatic Diseases, West London Hospital, physician, B.R.C.S. Clinic for Rheumatism, Peto Place, Hospital of St. John and Elizabeth and Cheyne Hospital for Children, and chairman of the Chartered Society for Physiotherapy and medical secretary, Empire Rheumatism Council. Fourth edition. 8°, cloth, 258 pp. Baltimore: The Williams and Wilkins Company, 1946. $4.00.

The Pathology of Nutritional Disease. By Richard H. Follis, Jr., M.D., associate professor of pathology, Duke University School of Medicine, Durham, North Carolina. 8°, cloth, 291 pp., with 71 illustrations. Springfield, Illinois: Charles C Thomas, 1947. $6.75.

NOTICES

ANNOUNCEMENT

Dr. Lewis S. Pilcher announces the removal of his office to 1180 Beacon Street, Brookline.

EXAMINATION FOR MEDICAL OFFICER POSITIONS

An examination has been announced by the United States Civil Service Commission for filling medical-officer positions at salaries ranging from $4479 to $6235 a year. The positions are located in Washington, D. C., throughout the United States and in the Panama Canal Zone, in such agencies as the Indian Service, Panama Canal Service, United States Public Health Service, Army, Veterans Administration, Civil Aeronautics Administration and Railroad Retirement Board.

No written test will be required. To qualify, applicants must be graduates of a medical school and must be currently licensed to practice medicine and surgery. (The requirement of a current license will be waived for certain persons and positions.) For positions paying $4479 and $5232, applicants must have completed a full internship, either general rotating or in a specialty (this requirement is waived for some positions); and for positions paying $5232 and $6235, they must have had professional medical experience. Maximum age limits for these positions are as follows: for Panama Canal Service, forty-five years; for Indian Service, fifty years; for other agencies, sixty-two years. For persons entitled to veteran preference, the forty-five-year and fifty-year age limits are waived to sixty-two years, and the sixty-two-year age limit is waived without limitation. Detailed information on requirements is given in the examination announcement.

Information and application forms may be obtained at most first-class and second-class post offices, from Civil Service regional offices or from the United States Civil Service Commission, Washington 25, D. C. Applications will be accepted in the Commission's Washington office until further notice.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

Meetings of Middlesex East District Medical Society will be held on the following dates: November 17, 1948 (Dr. Robert R. Linton will discuss the surgical and Dr. A. Stone Freedberg the medical aspect of "Thromboembolic Disease"); January 19, 1949 (discussion of medical, surgical and obstetric case, entitled "Stump the Experts"); March 23, 1949 (symposium on hypertension, with Dr. Lewis Dexter discussing the medical, Dr. J. C. White the surgical and Dr. Sanford H. Moses the obstetric aspects, and with Dr. George D. Bissell considering the general practitioner's problems); and May 11, 1949 ("Ladies' Night," with dancing and a selected speaker on a nonmedical subject).

AMERICAN CANCER SOCIETY, INCORPORATED

A medical symposium on the cancer problem will be held by the American Cancer Society, Incorporated, at the Hotel Commodore, New York City, on November 6 and 7. The program will include discussions on the following subjects: "The Cancer Problem Today"; "The Problem of Treatment—Recent Advances"; "The Problem of Cancer of the Lung"; and "Cancer Research, Cancer Education and the Cancer Problem in General Medical Practice."

AMERICAN FEDERATION FOR CLINICAL RESEARCH

The annual meeting of the Eastern Section of the American Federation for Clinical Research will be held at Temple University School of Medicine, Philadelphia, on Saturday, December 4.

INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA

The International Medical Assembly of the Interstate Postgraduate Medical Association of North America will be held in the Public Auditorium, Cleveland, Ohio, from November 9 to 12.

(Notices continued on page xv)